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(54) Title: 4,5,6,7–TETRAHYDRO–THIENO[3,2–c]PYRIDINE DERIVATIVES, THEIR PREPARATION AND USE

(57) Abstract

4,5,6,7–tetrahydro–thieno[3,2–c]pyridine derivative modulate the activity of molecules with glucose–6–phosphate recognition units, including glucose–6–phosphatases (G–6–Pases) in *in vitro* systems, microorganisms, eukaryotic cells, whole animals and human beings, and are useful in the treatment of diseases related to glucose metabolic pathways.

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4,5,6,7-Tetrahydro-thieno[3,2-c]pyridine Derivatives, their Preparation and Use

Field of the invention

The present invention relates to 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine derivatives, to methods for their preparation, to compositions comprising the compounds, to the use of these compounds as medicaments and their use in therapy, e.g. to their use for treatment of human and animal disorders.The invention relates to modulation of the activity of molecules with glucose-6-phosphate recognition units, including glucose-6-phosphatases (G-6-Pases) in *in vitro* systems, microorganisms, eukaryotic cells, whole animals and human beings, especially in the treatment of diseases related to glucose metabolic pathways.

Background of the invention

Glucose is the major energy substrate in mammals and regulation of blood glucose levels within a narrow range seems to be of crucial importance to devoid serious physiological complications as seen in diabetes (DeFronzo, Bonadonna, & Ferrannini. 1992). Blood glucose homeostasis is maintained by dietary intake of carbohydrates, the uptake of glucose by peripheral tissues and the brain, and storage or release of glucose from the liver. The liver therefore seems to play a major role in the homeostatic regulation of blood glucose levels. Gluconeogenesis and glycogenolysis are the two metabolic pathways from which glucose can be produced in the liver. These pathways are under tight hormonal control. Insulin resistance and insulin deficiency have a substantial impact on glucose production in the liver (Consoli. 1992; DeFronzo, Bonadonna, & Ferrannini. 1992; Clore, Stillman, Stevens, Blackard, Levy, & Richmond. 1996). Glucose-6-phosphatase (G-6-Pase) catalyses the terminal step in the above mentioned pathways by converting glucose-6-phosphate (G-6-P) to glucose, and is largely situated in the liver, with some expression in the kidney after prolonged fasting. The G-6-Pase is a multicomponent system comprising of the G-6-Pase catalytic enzyme with its active site located at the luminal site of the endoplasmic reticulum (microsomal fraction), a specific transporter T1 which mediates entry of G-6-P into the luminal compartment, and transporter T2 and T3 which mediates export to the cytosol of inorganic phosphate and glucose, respectively (Nordlie, Bode, & Foster. 1993; Sukalski & Nordlie. 1989). It has been shown that the rate of hydrolysis of G-6-P and the hepatic glucose output were increased under diabetic conditions (Lyall, Grant, Scott, & Burchell. 1992; DeFronzo, Bonadonna, & Ferrannini. 1992). The increased activity could mainly be accounted for by increased G-6-Pase catalytic enzyme protein (Argaud, Zhang, Pan, Maitra, Pilkis, &

Lange. 1996; Burchell & Cain. 1985). This makes G-6-Pase enzyme a potential target in control of excess glucose production seen in diabetes.

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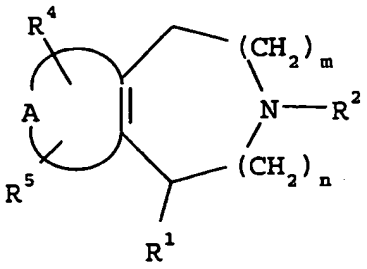
Description of the invention

The present invention relates to compounds of the general formula I:



(I)

wherein

A together with the double bond of formula I forms a cyclic system selected from the group consisting of benzene, thiophene, furan, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, indole, pyrazole, imidazole, oxazole, isoxazole or thiazole,

R^1 is C_{1-6}-alkyl, or aryl, optionally substituted with one or more substituents,

R^2 is C_{1-6}-alkyl, aralkyl, or COR^3 optionally substituted with one or more substituents,

R^3 is C_{1-6}-alkyl, aralkyl, or aryl, optionally substitued with one or more substituents,

R^4 and R^5 independently are hydrogen, halogen, perhalomethyl, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, nitro, cyano, amino, optionally substituted mono- or di-C_{1-6}-alkylamino, acylamino, C_{1-6}-alkoxycarbonyl, carboxy or carbamoyl,

n is 0, 1, or 2, and

m is 0, 1, or 2,

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

Within its scope the invention includes all isomers of compounds of formula I, some of which are optically active, and also their mixtures including racemic mixture thereof.

The scope of the invention also includes all tautomeric forms of the compounds of formula I.

The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts, such as hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, acetic, trifluoroacetic, trichloroacetic, oxalic, maleic, pyruvic, malonic, succinic, citric, tartaric, fumaric, mandelic, benzoic, cinnamic, methanesulfonic, ethanesulfonic, picric and the like, and include the pharmaceutically ac-

ceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) and incorporated herein by reference; pharmaceutically acceptable metal salts, such as lithium, sodium, potassium, or magnesium salts and the like; or - optionally alkylated - ammonium salts; or amine salts of the compounds of this invention, such as the sodium, potassium, C_{1-6}-alkylamine, di (C_{1-6}-alkyl) amine, tri (C_{1-6}-alkyl) amine and the four (4) corresponding omega-hydroxy analogues (e.g. methylamine, ethylamine, propylamine, dimethylamine, diethylamine, dipropylamine, trimethylamine, triethylamine, tripropylamine, di(hydroxyethyl)amine, and the like; Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present compounds are able to form. The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

The term "C_{1-6}-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated or unsaturated hydrocarbon chain. The C_{1-6}-alkyl residues include aliphatic hydrocarbon residues, unsaturated aliphatic hydrocarbon residues, alicyclic hydrocarbon residues. Examples of the aliphatic hydrocarbon residues include saturated aliphatic hydrocarbon residues having 1 to 6 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.butyl, tert.butyl, n-pentyl, isopentyl, neopentyl, tert.pentyl, n-hexyl, isohexyl. Example of the unsaturated aliphatic hydrocarbon residues includ those having 2 to 6 carbon atoms such as ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, ethynyl, 1-propionyl, 2-propionyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl. Examples of the alicyclic hydrocarbon residue include saturated alicyclic hydrocarbon residues having 3 to 6 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl; and C_{5-6} unsaturated alicyclic hydrocarbon residues having 5 to 6 carbon atoms such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl.

The terms "lower alkyl" and "lower alkoxy" mean C_{1-6}-alkyl and C_{1-6}-alkoxy, respectively.

The term "aryl" as used herein refers to an aryl which can be optionally substituted or a heteroaryl which can be optionally substituted and includes phenyl, biphenyl, indene, fluorene, naphthyl (1-naphthyl, 2-naphthyl), anthracene (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), pyrrolyl (2-pyrrolyl), pyrazolyl (e.g. 3-pyrazolyl, 4-pyrazolyl and 5-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3- pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benzoxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), furanyl (e.g. 2-furanyl, 3-furanyl, 4-furanyl and 5-furanyl), thienyl (e.g. 2-thienyl, 3-thienyl, 4-thienyl and 5-thienyl) optionally substituted with one or more substituents.

The term "optionally substituted" as used herein means an aryl residue as defined above or a C_{1-6}-alkyl residue as defined above that may be unsubstituted or may have 1 or more preferably 1 to 5 substituents, which are the same as or different from one another. Examples of these substituents include, halogen (fluorine, chlorine, bromine, iodine), hydroxyl, cyano, nitro, trifluoromethyl, carbamoyl, C_{1-4}-acyl (e.g. acetyl, propionyl, isopropionyl), C_{1-6}-alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, and tert.butoxy), C_{1-6}-alkyl as defined above, C_{1-6}-alkoxycarbonyl (e.g. ones having 2 to 6 carbon atoms such as methoxycarbonyl, ethoxycarbonyl, and propoxycarbonyl), C_{1-6}-alkanoyloxy (e.g. ones having 2 to 6 carbon atoms such as acetyloxy, propionyloxy, isopropionyloxy), C_{1-4}-alkylthio (e.g. ones having 1 to 4 carbon atoms such as methylthio, ethylthio, propylthio, and isopropylthio), C_{1-4}-alkylsulphinyl (e.g. ones having 1-4 carbon atoms such as methylsulphinyl and ethylsulphinyl), C_{1-4}-alkylsulphonyl (e.g. ones having 1-4 carbonatoms such as methylsulphonyl and ethylsulphonyl), C_{1-4}-alkylamino (e.g. one having 1 to 4 carbon atoms such as methylamino, ethylamino, dimethylamino, and 1-pyrrolidinyl), aminoalkyl (e.g. one having an amino containing group connected to a C_{1-6}-alkyl group as defined above, such as 2-dimethylaminoethyl and 1-pyrrolidinylmethyl), aminoalkoxy (e.g. one having an amino containing group connected via a C_{1-6}-alkyl group as defined above to an oxygen atom, such as 2-dimethylaminoethoxy, 2-(4-morpholinyl)ethoxy and 1-pyrrolidinylmethoxy), aryl as defined above (e.g. phenyl and 4-pyridinyl), aryloxy (e.g. phenyloxy), and aralkyloxy (e.g. benzyloxy).

The term "halogen" as used herein means fluorine, chlorine, bromine or iodine.

The term "perhalomethyl" as used herein means trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl.

The term "perhalomethoxy" as used herein means trifluoromethoxy, trichloromethoxy, tribromomethoxy or triiodomethoxy.

The term "aralkyl" as used herein refers to an optionally substituted aryl residue as defined above, connected to an optionally substituted C_{1-6}-alkyl as defined above. Examples of the aralkyl residue include benzyl, 2-phenylethyl, 2-phenylethenyl, 3-(2-pyridyl)propyl, 3-phenylpropyl, 1-naphtylmethyl, 2-(1-naphtyl)ethyl and the like.

The term "C_{1-6}-alkoxy" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a C_{1-6}-alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen and having 1 to 6 carbon atoms e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy.

The term "carbamoyl" as used herein refers to a carbamoyl which can be optionally substituted by one or two residues selected from the list consisting of optionally substituted C_{1-6}-alkyl as defined above, optionally substituted aryl as defined above and optionally substituted aralkyl as defined above.

In a preferred embodiment the invention relates to compounds of general formula (I) in which A is selected from benzene or thiophene.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R^1 is optionally substituted phenyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein each one of R^1, R^2, and R^3 is substituted with one or more substituents.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein the substituents of R^1 is halogen, perhalomethyl, perhalomethoxy, or C_{1-6}-alkoxy.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein the substituents of R^1 are selected from the group consisting of hydrogen, halogen, perhalomethyl, perhalomethoxy, or C_{1-6}-alkoxy.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein the substituents of R^1 are selected from from the group consisting of chloro, trifluoromethyl, methoxy, trifluoromethoxy.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R^1 is selected from the group consisting of phenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, and 4-trifluoromethoxyphenyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R^1 is 2,3-dihydrobenzofuran or 4-methoxyphenyl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R^2 is COR^3 or $(CH_2)_q$-aryl, and q is 0, 1, 2, 3, 4, 5, or 6.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R^3 is selected from the group consisting of phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-(2-dimethylaminoethoxy)phenyl, or 4-(2-morpholin-4-ylethoxy)phenyl.

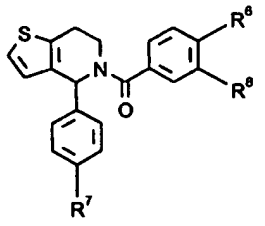
In another preferred embodiment the invention relates to compounds of general formula (I), wherein R^3 is selected from the group consisting of 4-methylphenyl, 3,4-dimethoxyphenyl, 4-ethoxyphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, dimethylaminophenyl, 4-(2-carboxyethenyl)phenyl, 4-(2-dimethylaminoethoxy)phenyl, 4-(2-morpholin-4-ylethoxy)phenyl, 1H-indol-5-yl, 3-chloro-4-methoxyphenyl, and 1H-benzimidazol-5-yl.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein R^4 and R^5 independently is hydrogen, chloro, or methoxy.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein n is 0 or 1 and m is 0 or 1.

In another preferred embodiment the invention relates to compounds of general formula (I), wherein n is 0 and m is or 1.

In a another preferred embodiment the invention relates to compounds of general formula (Ia):

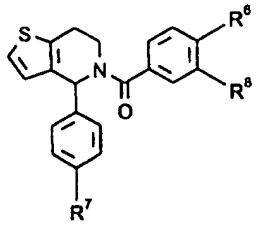


(Ia)

wherein R^7 is hydrogen, halogen, preferably chloro, methoxy, perhalomethoxy, preferably trifluoromethoxy, perhalomethyl, preferably trifluoromethyl, diloweralkylamino, preferably dimethylamino, or nitro,

and R^6 and R^8 independently are hydrogen, hydroxy, halogen, preferably chloro, bromo or fluoro, methyl, tert-butyl, phenyl, dimethylamino, methoxy, ethoxy, 2-dimethylaminoethoxy, 2-carboxyethenyl, 2-morpholin-4-ylethoxy, perhalomethyl, preferably trifluoromethyl, perhalomethoxy, preferably trifluoromethoxy, carboxy, cyano, methylthio, methylsulfonyl, acetamido, nitro, acetyl, acetoxy, or hydroxymethyl.

In another preferred embodiment the invention relates to compounds of general formula (Ia):



(Ia)

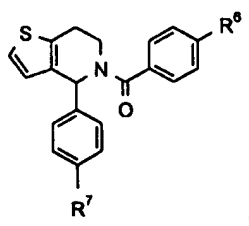
wherein R^7 is halogen, perhalomethyl, or perhalomethoxy

and R^6 and R^8 independently are hydrogen, methoxy, ethoxy, hydroxy, fluoro, chloro, bromo, iodo, methyl, trifluoromethyl, dimethylamino, 2-carboxyethenyl, 2-dimethylaminoethoxy, or 2-morpholin-4-ylethoxy.

R^7 is preferably selected from the group consisting of chloro, methoxy and trifluoromethyl, more preferably trifluoromethoxy.

Preferably, R^6 and R^8 are independently hydrogen, methoxy, chloro, trifluoromethyl, 2-dimethylaminoethoxy, or 2-morpholin-4-ylethoxy.

In another preferred embodiment the invention relates to compounds of general formula (Ib):

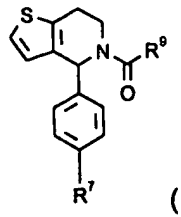


(Ib)

wherein R^7 is as described above, and

R^6 is hydroxy, halogen, preferably chloro or fluoro, methyl, dimethylamino, methoxy, ethoxy, perhalomethyl, preferably trifluoromethyl, perhalomethoxy, preferably trifluoromethoxy, cyano, methylthio, acetyl, acetoxy, or hydroxymethyl.

In another preferred embodiment the invention relates to compounds of general formula (Ic):

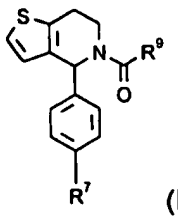


(Ic)

wherein R^7 is as defined above, and

R^9 is 4-pyridyl, 5-hydroxypyrazin-2-yl, 5-chloro-6-hydroxypyridin-3-yl, 2-chloropyridin-3-yl, benzofuran-2-yl, benzothiophen-2-yl-, 7-methoxybenzofuran-2-yl, indolyl, preferably 1H-indol-5-yl, benzimidazol, preferably 1H-benzimidazol-5-yl or thienyl, preferably 5-chlorothiophen-2-yl.

In another preferred embodiment the invention relates to compounds of general formula (Ic):

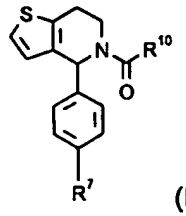


(Ic)

wherein R^7 is as defined above and R^9 is indolyl, preferably 1H-indol-5-yl or benzimidazol, preferably 1H-benzimidazol-5-yl.

In the compounds of formula (Ic) R^9 is preferably benzothiophen-2-yl, indolyl, preferably 1H-indol-5-yl, or benzimidazol, preferably 1H-benzimidazol-5-yl.

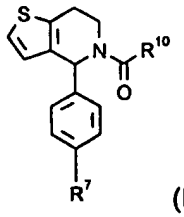
In another preferred embodiment the invention relates to compounds of general formula (Id):



(Id)

wherein R^7 is as defined above, and R^{10} is optionally substituted aralkyl as defined above, preferably 2-(4-methoxyphenyl)-ethenyl, 2-(3-methoxyphenyl)-ethenyl, 2-(4-chlorophenyl)-ethenyl, 2-(4-fluorophenyl)-ethenyl, 2-(4-trifluoromethylphenyl)-ethenyl, 2-(4-methoxyphenyl)-ethyl, 2-(4-chlorophenyl)-ethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-(2-furyl)-ethenyl, 2-(4,5-dimethyl-2-furyl)-ethenyl, 2-(5-methyl-2-furyl)-ethenyl, 2-(3-furyl)-ethenyl, 2-(2-thienyl)-ethenyl, or 2-(3-thienyl)-ethenyl.

In another preferred embodiment the invention relates to compounds of general formula (Id):

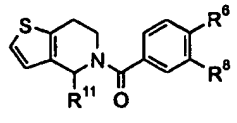


(Id)

wherein R^7 is as defined above, and R^{10} is 4-methoxyphenyl-2-ethenyl.

In the compounds of formula (Id) R^7 is preferably as defined above and R^{10} is optionally substituted aralkyl as defined above, preferably 2-(4-methoxyphenyl)-ethenyl, 2-(2-furyl)-ethenyl, 2-(5-methyl-2-furyl)-ethenyl, 2-(3-furyl)-ethenyl, or 2-(3-thienyl)-ethenyl.

In another preferred embodiment the invention relates to compounds of general formula (Ie):



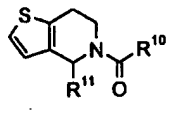
(Ie)

wherein R^{11} is pyridyl, preferably 4-pyridyl, and

R^6 and R^8 independently are hydrogen, hydroxy, halogen, preferably chloro, bromo or fluoro, methyl, tert-butyl, phenyl, dimethylamino, methoxy, ethoxy, 2-dimethylaminoethoxy, 2-carboxyethenyl, 2-morpholin-4-ylethoxy, perhalomethyl, preferably trifluoromethyl, perhalo-

methoxy, preferably trifluoromethoxy, carboxy, cyano, methylthio, methylsulfonyl, acetamido, nitro, acetyl, acetoxy, or hydroxymethyl.

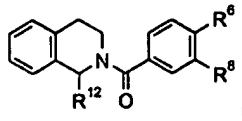
In another preferred embodiment the invention relates to compounds of general formula (If):



(If)

wherein R^{10} is optionally substituted aralkyl as defined above, preferably 2-(4-methoxyphenyl)-ethenyl, 2-(3-methoxyphenyl)-ethenyl, 2-(4-chlorophenyl)-ethenyl, 2-(4-fluorophenyl)-ethenyl, 2-(4-trifluoromethylphenyl)-ethenyl, 2-(4-methoxyphenyl)-ethyl, 2-(4-chlorophenyl)-ethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-(2-furyl)-ethenyl, 2-(4,5-dimethyl-2-furyl)-ethenyl, 2-(5-methyl-2-furyl)-ethenyl, 2-(3-furyl)-ethenyl, 2-(2-thienyl)-ethenyl, or 2-(3-thienyl)-ethenyl, and R^{11} is pyridyl, preferably 4-pyridyl.

In another preferred embodiment the invention relates to compounds of general formula (Ig):

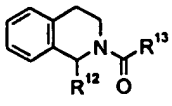


(Ig)

wherein R^{12} is aryl or aralkyl, and

R^6 and R^8 independently are hydrogen, hydroxy, halogen, preferably chloro, bromo or fluoro, methyl, tert-butyl, phenyl, dimethylamino, methoxy, ethoxy, 2-dimethylaminoethoxy, 2-carboxyethenyl, 2-morpholin-4-ylethoxy, perhalomethyl, preferably trifluoromethyl, perhalomethoxy, preferably trifluoromethoxy, carboxy, cyano, methylthio, methylsulfonyl, acetamido, nitro, acetyl, acetoxy, or hydroxymethyl.

In another preferred embodiment the invention relates to compounds of general formula (Ih):



(Ih)

wherein R^{12} is aryl, preferably 4-trifluoromethoxyphenyl, or aralkyl, preferably benzyl, and

R^{13} is aralkyl as defined above, preferably 2-(4-methoxyphenyl)-ethenyl, 2-(3-methoxyphenyl)-ethenyl, 2-(4-chlorophenyl)-ethenyl, 2-(4-fluorophenyl)-ethenyl, 2-(4-trifluoromethylphenyl)-ethenyl, 2-(4-methoxyphenyl)-ethyl, 2-(4-chlorophenyl)-ethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-(2-furyl)-ethenyl, 2-(4,5-dimethyl-2-furyl)-ethenyl, 2-(5-methyl-2-furyl)-ethenyl, 2-(3-furyl)-ethenyl, 2-(2-thienyl)-ethenyl, or 2-(3-thienyl)-ethenyl.

The most preferred compounds of the invention are:

(+)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 1),
(-)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 2),
(+)-[4-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-trifluoromethylphenyl)-methanone, (compound No. 3),
(-)-[4-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-trifluoromethylphenyl)-methanone, (compound No. 4),
[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 5),
(+)-[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 6),
(-)-[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 7),
[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(3-methoxyphenyl)-methanone, (compound No. 8),
(+)-[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(3-methoxyphenyl)-methanone, (compound No. 9),
(-)-[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(3-

methoxyphenyl)-methanone, (compound No. 10),
[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-phenyl-methanone, (compound No. 11),
(+)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-phenyl-methanone, (compound No. 12),
(-)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-phenyl-methanone, (compound No. 13),
(4-(2-Dimethylaminoethoxy)phenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 14),
(+)-(4-(2-Dimethylaminoethoxy)phenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 15),
(-)-(4-(2-Dimethylaminoethoxy)phenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 16),
[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-(2-[2-morpholin-4-ylethoxy)phenyl]-methanone, (compound No. 17),
(+)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-(2-[2-morpholin-4-ylethoxy)phenyl]-methanone, (compound No. 18),
(-)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-(2-[2-morpholin-4-ylethoxy)phenyl]-methanone, (compound No. 19),
[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-dimethylaminophenyl)-methanone, (compound No 20),
3-{4-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]phenyl}acrylic acid, (compound No 21),
(4-Chlorophenyl)-[4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, both the racemate, the two pure enantiomers, and mixtures thereof (compound No 22),
[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 24),
[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 25),
[4-(2-Dimethylaminoethoxy)-phenyl]-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 26),
[4-(2-Dimethylaminoethoxy)-phenyl]-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 27),
[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-[4-(2-morpholin-4-

ylethoxy)phenyl]-methanone, (compound No. 28),
[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-[4-(2-morpholin-4-ylethoxy)phenyl]-methanone, (compound No. 29),
[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 30),
[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 31),
[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 32),
[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(1H-indol-5-yl)-methanone, (compound No. 33),
(1H-Indol-5-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 34),
[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-fluorophenyl)-methanone, (compound No. 35),
[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-fluorophenyl)-methanone, (compound No. 36),
4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-[4-(2-dimethylaminoethoxy)phenyl]-methanone, (compound No. 37),
[4-(2-Dimethylaminoethoxy)phenyl]-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 38),
[7-Chloro-1-(2,3-dihydrobenzofuran-7-yl)-8-methoxy-1,2,4,5-tetrahydrobenzo[d]azepin-3-yl]-[4-(2-dimethylaminoethoxy)-phenyl]-methanone, (compound No. 39),
[4-(3,4-Dimethoxyphenyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-6-yl]-[4-(2-dimethylaminoethoxy)-phenyl]-methanone, (compound No. 40),
(3,4-Dimethoxyphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 41),
(3-Chloro-4-methoxyphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 42),
(4-Ethoxyphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 43),
(4-Methylphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 44),
3-(4-Methoxyphenyl)-1-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-

5-yl]propenone, (compound No. 45),
(1H-Benzimidazol-5-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 46),
(4-Methoxyphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone
[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone
[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methylsulfanylphenyl)-methanone
4-[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]benzoic acid methyl ester
(4-Hydroxymethylphenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone
(4-Acetoxyphenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone
(4-Cyanophenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone
1-{4-[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]phenyl}ethanone
3-Furan-2-yl-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone
3-(5-Methylfuran-2-yl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone
Benzo[b]thiophen-2-yl-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone
3-Furan-3-yl-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone
3-Thiophen-3-yl-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone
3-Thiophen-2-yl-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone
[4-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methylsulfanylphenyl)methanone
4-[4-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]benzonitrile

3-Furan-3-yl-1-[4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone

(4-Methoxyphenyl)-[4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

(4-Fluorophenyl)-[4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

(4-Chlorophenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

(4-Methylsulfanylphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

(4-Dimethylaminophenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

(4-Hydroxymethylphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

3-Furan-3-yl-1-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone

4-(4-Chlorophenyl)-5-(4-methoxybenzyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine hydrochloride

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-hydroxyphenyl)methanone

1-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-(4-methoxyphenyl)ethanone

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(3-dimethylaminophenyl)methanone

N-{4-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]-phenyl}acetamide

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methanesulfonylphenyl)methanone

2-(4-Chlorophenyl)-1-[4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]ethanone

2-(4-Methoxyphenyl)-1-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone

(3-Dimethylaminophenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone

N-{4-[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]-phenyl}-acetamide

(4-Methanesulfonylphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone

2-(4-Chlorophenyl)-1-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone

Biphenyl-4-yl-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

(3,4-Dichlorophenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

(4-tert-Butylphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

Pyridin-4-yl-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

(5-Hydroxypyrazin-2-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

(5-Chloro-6-hydroxypyridin-3-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

3-(4,5-Dimethylfuran-2-yl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone

(1-Benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)-(4-methoxyphenyl)methanone

(1-Benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)-(4-chlorophenyl)methanone

(1H-Benzoimidazol-5-yl)-(1-benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)methanone

1-(1-Benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)-3-furan-3-ylpropenone

1-(1-Benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)-3-(4-methoxyphenyl)propenone

1-(1-Benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)-3-(4-methoxyphenyl)propan-1-one

1-(1-Benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)-2-(4-methoxyphenyl)ethanone

(5-Chlorothiophen-2-yl)-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)methanone

(5-Chlorothiophen-2-yl)-[4-(4-dimethylaminophenyl)4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

(5-Chlorothiophen-2-yl)-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)methanone

(4-Hydroxymethylphenyl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)methanone

[4-(4-Dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-(4-hydroxymethylphenyl)-methanone

[4-(4-Nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-(4-hydroxymethylphenyl)-methanone

(4-Chlorophenyl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)methanone

(4-Chlorophenyl)-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

(4-Chlorophenyl)-[4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

(4-Chlorophenyl)-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

(4-Methoxyphenyl)-[4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

(4-Methoxyphenyl)-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

[4-(4-Dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone

[4-(4-Dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone

3-(4-Methoxyphenyl)-1-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-propenone

(5-Chlorothiophen-2-yl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

3-(4-Methoxyphenyl)-1-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-propenone

1-[4-(4-Dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-3-(4-methoxyphenyl)-propenone

3-(4-Methoxyphenyl)-1-(4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-propenone

(4-Dimethylaminophenyl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

(4-Dimethylaminophenyl)-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

(4-Dimethylaminophenyl)-[4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone

(4-Dimethylaminophenyl)-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone

(1H-Benzoimidazol-5-yl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

(1H-Benzoimidazol-5-yl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

(1H-Benzoimidazol-5-yl)-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone

(4-Fluorophenyl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

(4-Fluorophenyl)-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

[4-(4-Dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-fluorophenyl)-methanone

(4-Fluorophenyl)-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone

(4-Bromophenyl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

(4-Bromophenyl)-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

(4-Bromophenyl)-[4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone

(4-Bromophenyl)-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

3-Furan-3-yl-1-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-propenone

3-(3-Furan-3-yl)-1-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-propenone

1-[4-(4-Dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-3-(3-furan-3-yl)-propenone

3-(3-Furan-3-yl)-1-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-propenone

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-hydroxyphenyl)-methanone, less polar enantiomer,

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-hydroxyphenyl)-methanone, more polar enantiomer,

(1H-Benzoimidazol-5-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, less polar enantiomer,

(1H-Benzoimidazol-5-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, more polar enantiomer,

(5-Chlorothiophen-2-yl)-[1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]-methanone

(4-Chlorophenyl)-[1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]-methanone

(4-Methoxyphenyl)-[1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]-methanone

3-(4-Methoxyphenyl)-1-[1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]propenone

3-Furan-3-yl-1-[1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]propenone

(4-Trifluoromethoxyphenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

(7-Methoxybenzofuran-2-yl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

Benzofuran-2-yl-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

3-(4-Fluorophenyl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-propenone

3-(4-Trifluoromethylphenyl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone

3-(3-Methoxyphenyl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone

3-(4-Chlorophenyl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone

3-(4-Methoxyphenyl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propan-1-one

3-(4-Chlorophenyl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propan-1-one

and salts thereof with a pharmaceutically acceptable acid or base.

The compounds of the present invention are normoglycaemic agents (i.e. compounds that are able to normalise blood glucose levels from hyper-/hypoglycemic conditions) that interact with the glucose-6-phosphatase catalytic enzyme activity, and hence make them useful in the treatment and prevention of various diseases of the endocrinological system, especially ailments related to carbohydrate metabolism and especially the glucose metabolism, e.g. hyperglycaemia, diabetes mellitus, and especially non-insulin dependent diabetes mellitus (NIDDM) including long-term complications, such as retinopathy, neuropathy, nephropathy, and micro- and macroangiopathy, and hypoglycaemia resulting from, e.g., glycogen storage disease (von Gierke's Disease all types). Moreover, the present compounds are useful in the prophylactic treatment of hyperlipidaemia, hypertension, liver and bile diseases, and atherosclerosis associated with diabetes. The present compounds are especially useful in the treatment of diseases associated with an increased or reduced activity of the glucose-6-phosphatase complex, e. g. the G-6-Pase catalytic enzyme.

Accordingly, in another aspect the invention relates to a compound of the general formula I, Ia, Ib, Ic or a pharmaceutically acceptable acid addition salt or other salt as defined above thereof for use as a therapeutically acceptable substance, preferably for use as a therapeuti-

cally acceptable substance in the treatment of hyperglycaemia and treatment or prevention of diabetes.

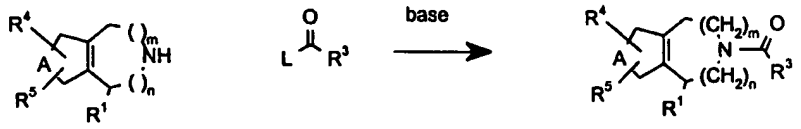
Furthermore, the invention also relates to the use of the inventive compounds of formula I, Ia, Ib, and Ic as medicaments useful for treating hyperglycaemia and treating or preventing diabetes.

In yet another aspect, the present invention relates to methods of preparing the above mentioned compounds. Methods of preparing compounds of general formula I comprises:

Method A:

When R^2 is COR^3:

Reacting a compound of formula X with a compound of formula Y to form compounds of general formula Ib:



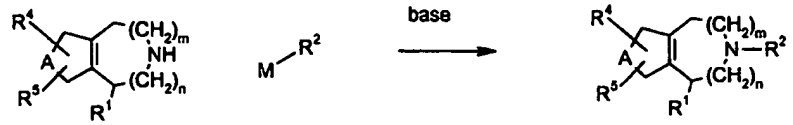
X Y Ib

wherein R^1, R^3, R^4, R^5, n, and m are as defined above and L is a leaving group and are selected from fluorine, chlorine, bromine, iodine, 1-imidazolyl, 1,2,4-triazolyl, 1-benzotriazolyloxy, 1-(4-aza benzotriazolyl)oxy, pentafluorophenoxy, N-succinyloxy 3,4-dihydro-4-oxo-3-(1,2,3-benzotriazinyl)oxy, R^3COO where R^3 is as defined above, or any other leaving group known to act as a leaving group in acylation reactions. The base can be either absent (i.e. compound X acts as a base) or triethylamine, N-ethyl-N,N.-diisopropylamine, N-methylmorpholine, 2,6-lutidine, 2,2,6,6-tetramethylpiperidine, potassium carbonate, sodium carbonate, caesium carbonate or any other base known to be useful in acylation reactions.

Method B:

When R^2 is optionally substituted C_{1-6} alkyl or aralkyl:

a) Reacting a compound of formula X with a compound of formula Z in an alkylation reaction to form compounds of general formula I:

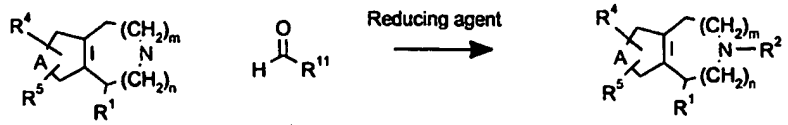


X Z I

wherein R^1, R^2, R^4, R^5, n, and m are as defined above, M is a leaving group and is selected from chlorine, bromine, iodine, methanesulfonyloxy, trifluoromethanesulfonyloxy, p-toluenesulfonyloxy or any other group known to act as a leaving group in alkylation reactions. The base can be either absent (i.e. compound X acts as a base) or triethylamine, N-ethyl-N,N.-diisopropylamine, N-methylmorpholine, 2,6-lutidine, 2,2,6,6-tetramethylpiperidine, potassium carbonate, sodium carbonate, caesium carbonate or any other base known to be useful in alkylation reactions.

Method C :

Reacting a compound of formula X with an aldehyde of formula Zz in a reductive alkylation reaction to form compounds of general formula I:



X Zz I

wherein R^1, R^2, R^4, R^5, n, and m are as defined above, R^{11} is as defined for R^2 but one (1) carbon atom shorter. The reducing agent can be selected from the following list: $NaCNBH_3$, $NaBH(OAc)_3$, diborane, BH_3 complexes (eg. with tetrahydrofuran or dimethylsulfide), metallic

sodium, or H_2/catalyst or any reductant known to be effective in the reductive alkylation reaction.

Or the compounds of formulae I, Ia, Ib, and Ic may be prepared by art-recognized procedures from known compounds or readily preparable intermediates.

The starting materials are either known compounds or compounds which may be prepared in analogy with the preparation of known compounds or in analogy with known methods as described by e.g Tupper D.E. et al., *J. Heterocyclic Chem.*, 33, 1123-9 (1996), Stokker G.E., *Tetrahedron Lett.*, 37, 5453-6 (1996), Nakagawa, M. et al., *Chem. Pharm. Bull.*, 41, 287-91 (1993), Singh H. et al., *Heterocycles*, 23, 107-10 (1985), Skinner W.A. et al., *Can. J. Chem.*, 43, 2251-3 (1965). P. Kumar et al., *J. Heterocyclic Chem.*, **19**, 677-9 (1982), L. K. Lukanov et al., *Synthesis*, **1987**, 204-6, A. L. Stanley & S. P. Stanforth, *J. Heterocyclic Chem.*, **31**, 1399-1400 (1994), A. K. Bose et al., *J. Org. Chem.*, **56**, 6968-70 (1991), K. Kementani et al., *Heterocycles*, **3**, 311-41 (1975), E. Domonguez et al., *Tetrahedron*, **43**, 1943-8 (1987), J. B. Bremner et al., Aust. J. Chem., 41, 1815-26 (1988), M. J. O'Donnel et al., *Tetrahedron. Lett.*, **23**, 4259-62 (1982).

Pharmacological methods

The ability of compounds to inhibit glucose-6-phosphatase (G-6-Pase) catalytic enzyme activity from pig liver microsomes was tested in the following way:

Pig liver microsomes were prepared in a buffer containing 250 mM sucrose, 1 mM EDTA, 25 mM HEPES and 250 mg/l Bacitrazin (pH 7.5) essentially as described by Arion et al.,1980 (Arion, Lange, & Walls. 1980). Microsomes were kept at -80 °C until use.

Prior to measurement microsomes were treated with Triton X-100 (0.04%) ("disrupted microsomes"). G-6-Pase activity were assayed for 6 min at 30°C in a total volume of 325 µL containing 0.5 mM glucose-6-phosphate, 30 mM MES (pH 6.5), test compound and disrupted microsomes (0.05 mg). The reaction was terminated by addition of 100 µL Sigma phosphorus reagent (cat no 360-3C). This mixture was allowed to stand for 2 min, where the absorbance (A) was measured at 340 nm. All values were corrected for blank. The inhibitory effect was expressed as percent of control value, i.e. IC_{50} is the concentration of a compound that produces 50% inhibition.

The compounds of the invention are preferably characterized by having a glucose-6-phosphatase inhibitory activity corresponding to an IC_{50} value of less than 100 μM, more preferably less than 10 μM, even more preferably less than 1 μM, still more preferably less than 100 nM.

The compounds according to the invention are effective over a wide dosage range. In general satisfactory results are obtained with dosages from about 0.05 to about 1000 or 5000mg, preferably from about 0.1 to about 500 mg, per day. A most preferable dosage is about 5 mg to about 200 mg per day. The exact dosage will depend upon the mode of administration, form in which the compound is administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

The dosage unit of the pharmaceutical compositions according to the invention typically contains from 0.05mg to 1000mg, preferably from 0.1mg to 500mg, or, preferably from 5mg to 200mg per day of the active ingredient, which is, preferably, a novel 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine derivative as described herein or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form thereof; or the active ingredient is a previously described 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine derivative or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form thereof.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intrapulmonary, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

Optionally, the pharmaceutical composition of the invention may comprise a compound of formula I combined with one or more compounds exhibiting a different activity, e.g., a plasma lipid

lowering compounds, sulphonylurea like compounds, or other oral agents useful in the treatment of diabetes, or other pharmacologically active material.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of formula I or a pharmaceutically acceptable acid addition salt or metal salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated in any galenic dosage form so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art. The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For administration, preferably nasal administration, the preparation may contain a compound of formula I, Ia, Ib or Ic dissolved or suspended in a liquid carrier, in particular an aqueous car-

rier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes. For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil. Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet, appropriate for use in this method, may be prepared by conventional tabletting techniques and contains:

Core:	
Active compound (as free compound or salt thereof)	5.0 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	**Ad.**
Coating:	
HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

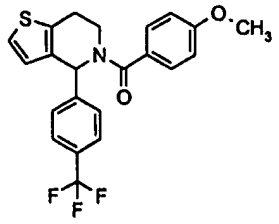
Due to their high degree of activity, the compounds of the invention may be administered to a mammal in need of such treatment, prevention, elimination, alleviation or amelioration of various diseases as mentioned above and especially of diseases of the endocrinological system such as hyperinsulinaemia and diabetes. Such mammals include both domestic animals, e.g. household pets, and non-domestic animals such as wildlife. Preferably the mammal is a human.

EXAMPLES

The process for preparing compounds of formula I, Ia, Ib, and/or Ic and preparations containing them is further illustrated in the following examples which, however, are not to be construed as limiting.

EXAMPLE 1

Preparation of
[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 5)

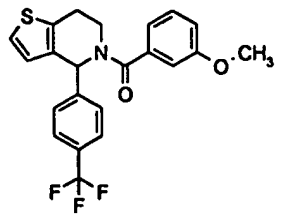


4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (100 mg, 0.35 mmol) was dissolved in dichloromethane (0.5 mL) and triethylamine (0.5 mL) was added. To this solution p-anisoyl chloride (60 mg, 0.35 mmol) dissolved in dichloromethane (0.5 ml) was added in one portion. The mixture was filtered and evaporated to afford 148 mg (100%) of the title compound.

MS (electrospray):	m/z 418 (M+1)
HR-MS:	Calculated for $C_{22}H_{18}F_3NO_2S$: 417.1010, Found: 417.0999.

EXAMPLE 2:

Preparation of
[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(3-methoxyphenyl)-methanone, (compound No. 8)



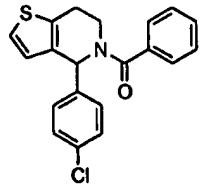
4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (100 mg, 0.35 mmol) was dissolved in dichloromethane (1 mL) and diisopropylethylamine (0.5 mL) was added. To this solution m-anisoyl chloride (50 µL, 0.35 mmol) was added. The mixture was shaken overnight and evaporated to afford the title compound.

MS (electrospray): m/z 418 (M+1)

HR-MS: Calculated for $C_{22}H_{18}F_3NO_2S$: 417.1010, Found: 417.1020.

EXAMPLE 3:

Preparation of [4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-phenyl-methanone, (compound No 11)



Benzoic acid (46 mg, 0.38 mmol) and 1-hydroxybenzotriazole (55 mg, 0.41 mmol) were dissolved in a mixture of dichloromethane (1 mL) and N,N-dimethylformamide (0.5 mL). N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (79 mg, 0.41 mmol) was added and the mixture was shaken 0.5 hour at room temperature. 4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (100 mg, 0.38 mmol) dissolved in dichloromethane (0.5 ml)

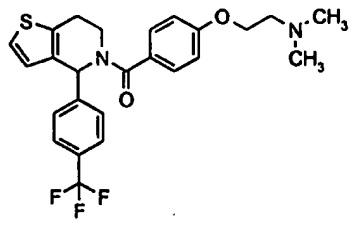
was added and the mixture was shaken at 1000 rpm for 3 hours. Water (1 mL) was added and the mixture was shaken at 1000 rpm overnight at room temperature. The organic phase was evaporated to give 129 mg (97%) of the title compound as an oil.

MS (electrospray): m/z 354 (M+1)

HR-MS: Calculated for $C_{20}H_{16}ClNOS$: 353.0641, Found: 353.0646.

EXAMPLE 4:

Preparation of (4-(2-Dimethylaminoethoxy)phenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No 14)



Methyl 4-hydroxybenzoate (10 g, 66 mmoles) was dissolved in N,N-dimethylformamide (200 mL). Potassium carbonate (45 g, 0.33 moles) and 2-chloro-N,N-dimethylethylamine hydrochloride (14.2 g, 99 mmoles) were added and the resulting mixture was stirred vigorously at room temperature for 7 days. More 2-chloro-N,N-dimethylethylamine hydrochloride (3 g, 20 mmoles) was added and stirring at room temperature was continued for 2 days. The reaction mixture was poured into water (600 mL) and extraction with ethyl acetate (2 x 200 mL), washing of the combined organic phases with water (200 mL), drying over $MgSO_4$ and evaporation afforded 11.9 g (81%) of methyl 4-(2-dimethylaminoethoxy)benzoate as an oil.

The above benzoate (11.9 g, 53 mmoles) was dissolved in 5 N hydrochloric acid and the mixture was heated at reflux temperature for 2 days. Cooling, filtration and washing with water afforded 8.63 g (66%) of 4-(2-dimethylaminoethoxy)benzoic acid hydrochloride as crystals.

The above benzoic acid (93 mg, 0.38 mmoles) was suspended in N,N-dimethylformamide (1 mL). 1-Hydroxybenzotriazole (55 mg, 0.42 mmoles), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (79 mg, 0.42 mmoles), and triethylamine (106 µL, 0.76 mmoles) were added and the resulting mixture was shaken at 1000 rpm for 1.5 hour. 4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (108 mg, 0.38 mmoles) were added and the resulting mixture was shaken at 1000 rpm for 3 hours. Water (2 mL) and ethyl acetate (1 mL) were added and the resulting mixture was shaken at 1000 rpm for 15 minutes. The organic phase was evaporated to afford 144 mg (80%) of the title compound as an oil.

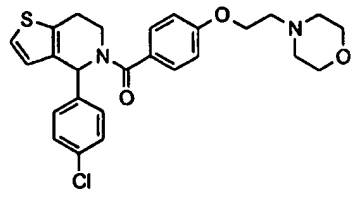
MS (electrospray): m/z 475.0 (M+1)

HR-MS: Calculated for $C_{25}H_{25}F_3N_2O_2S$: 474.1588, Found: 474.1580.

EXAMPLE 5:

Preparation of

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-[4-(2-morpholin-4-ylethoxy)phenyl]-methanone, (compound No 17)



Methyl 4-hydroxybenzoate (10 g, 66 mmoles) was dissolved in N,N-dimethylformamide (200 mL). Potassium carbonate (45 g, 0.33 moles) and 4-(2-chloroethyl)morpholine hydrochloride (18.3 g, 99 mmoles) were added and the resulting mixture was stirred vigorously at room temperature for 5 days. The reaction mixture was poured into water (500 mL) and extraction with ethyl acetate (2 x 250 mL), washing of the combined organic phases with water (200 mL), drying over $MgSO_4$ and evaporation afforded 16.8 g (96%) of methyl 4-(2-morpholin-4-ylethoxy)benzoate as an oil.

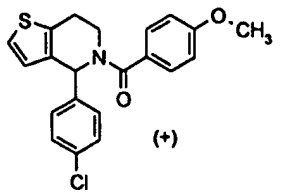
The above benzoate (16.8 g, 63 mmoles) was dissolved in 5 N hydrochloric acid and the mixture was heated at reflux temperature for 16 hours. Cooling, filtration and washing with water afforded 15.6 g (86%) of 4-(2-morpholin-4-ylethoxy)benzoic acid hydrochloride as crystals.

The above benzoic acid (111 mg, 0.38 mmoles) was suspended in N,N-dimethylformamide (1 mL). 1-Hydroxybenzotriazole (55 mg, 0.42 mmoles), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (79 mg, 0.42 mmoles), and triethylamine (106 µL, 0.76 mmoles) were added and the resulting mixture was shaken at 1000 rpm for 1.5 hour. 4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (100 mg, 0.38 mmoles) was added and the resulting mixture was shaken at 1000 rpm for 3 hours. Water (2 mL) and ethyl acetate (1 mL) were added and the resulting mixture was shaken at 1000 rpm for 15 minutes. The organic phase was evaporated to afford 122 mg (66%) of the title compound as an oil.

MS (electrospray):	m/z 483.0 (M+1)
HR-MS:	Calculated for $C_{26}H_{27}ClN_2O_3S$: 482.1431, Found: 482.1430.

EXAMPLE 6:

Preparation of
(+)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No 1)



(+)

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone (30 mg) was dissolved in a 1:1 mixture of n-heptane and 2-propanol (5 mL) and fractionated by HPLC (2 runs) using a 21.1 x 250 mm (*R,R*)-Whelk-O column (Regis). The

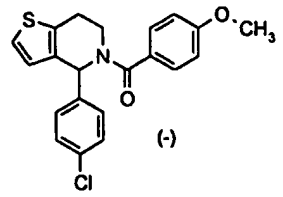
column was eluted isocratically with a 1:1 mixture of n-heptane and 2-propanol at a flow rate of 12 mL/min and fractions collected corresponding to 0.8 min/fraction. The eluting enantiomers were detected spectroscopically by measuring absorbance at a wavelength of 225 nm. Two eluting peaks were detected, one corresponding to T_R 44-50 min and one corresponding to T_R 62-72 min. Fractions from the two runs corresponding to T_R 44-50 min were separately pooled and evaporated to yield 12.1 mg of the title compound.

100% ee (Determined by HPLC using a 4.6 x 250 mm (*R,R*)-Whelk-O column eluted with a 1:1 mixture of n-heptane and 2-propanol, the flow rate was 1 ml/min, eluting sample was monitored spectroscopically at 225 and 245 nm, T_R 15.5 min).

EXAMPLE 7:

Preparation of

(-)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No 2)



(-)

Fractions from the two runs of example 6 corresponding to T_R 62-72 min were separately pooled and evaporated to yield 12.5 mg of the title compound

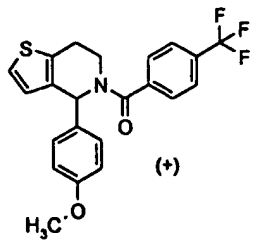
98% ee (Conditions as described in example 6, T_R 20.8 min).

Optical rotation, using a Perkin Elmer Polarimeter (Model 241):

$[\alpha]^{20}_D$= - 170.0 (c=0.25, ethyl acetate).

EXAMPLE 8:

Preparation of
(+)-[4-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-trifluoromethylphenyl)-methanone, (compound No 3)



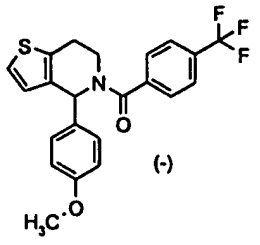
[4-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-trifluoromethylphenyl)-methanone (17 mg) was dissolved in a 1:2:2 mixture of ethyl acetate, n-heptane and 2-propanol (2.5 mL) and fractionated by HPLC using a 21.1 x 250 mm (*R,R*)-Whelk-O column (Regis). The column was eluted isocratically with a 1:1 mixture of n-heptane and 2-propanol at a flow rate of 10 mL/min and fractions collected corresponding to 1 min/fraction. The eluting enantiomers were detected spectroscopically by measuring absorbance at a wave-length of 225 nm. Two eluting peaks were detected, one corresponding to T_R 27-32 min and one corresponding to T_R 62-74 min. Fractions corresponding to T_R 27-32 min were pooled and evaporated to yield 7.1 mg of the title compound.

100% ee (Determined by HPLC using a 4.6 x 250 mm (*R,R*)-Whelk-O column eluted with a 1:1 mixture of n-heptane and 2-propanol, the flow rate was 1 mL/min, eluting sample was monitored spectroscopically at 225 and 245 nm, T_R 9.2 min)

Optical rotation, using a Perkin Elmer Polarimeter (Model 241),
$[\alpha]^{20}_D$= + 175.4 (c=0.142, ethyl acetate).

EXAMPLE 9:

Preparation of
(-)-[4-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-trifluoromethylphenyl)-methanone, (compound No 4)



(-)

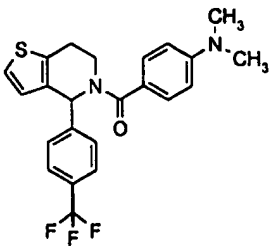
Fractions from the two runs of example 8 corresponding to T_R 62-74 min were separately pooled and evaporated to yield 6.8 mg of the title compound.

>99.5% ee (Conditions as described in example 8, T_R 17.0 min).

$[\alpha]^{20}_D$= - 170.6 (c=0.136, ethyl acetate).

EXAMPLE 10:

[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-dimethylaminophenyl)-methanone, (compound No 20)



4-Dimethylaminobenzoic acid (0.20 g, 1.2 mmol) was dissolved in N,N-dimethylformamide (3 ml) and 1-hydroxybenzotriazole (0.20 g, 1.5 mmol) was added. To the resulting mixture N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.28 g, 1.5 mmol) was added and the mixture was stirred at room temperature for 15 minutes. 4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (0.41 g, 1.5 mmol) followed by diisopropylethylamine (0.42 ml, 2.4 mmol) were added and the mixture was stirred at room temperature for 16 hours. water (2 ml) was added and the mixture was extracted with ethyl acetate (2 x 5 ml).

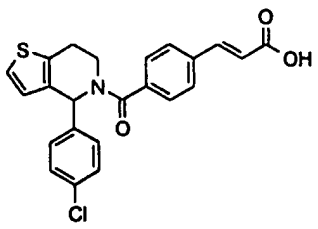
The combined organic extracts were washed with saturated aqueous sodium chloride solution (4 ml), dried ($MgSO_4$) and concentrated in vacuo to afford the title compound.

MS (electrospray): m/z 431 (M+1)

HPLC (Method B): R_t = 29 min.

EXAMPLE 11:

3-{4-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]phenyl}acrylic acid, (compound No 21)



(E)-4-(2-tert-Butoxycarbonylvinyl)benzoic acid (0.36 g, 1.4 mmol) was dissolved in N,N-dimethylformamide (50 ml) and 1-hydroxybenzoetriazole (0.20 g, 1.4 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.28 g, 1.4 mmol) were added and the mixture was stirred at room temperature for 20 minutes. 4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (0.30 g, 1.2 mmol) and N-ethyl-N,N-diisopropylamine (420 µl, 2.4 mmol) were added to the mixture and stirring at room temperature was continued for 16 hours. The mixture was diluted with water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with saturated sodium chloride (80 ml), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by coloumn chromatography over silica gel (60 ml) eluting with a mixture of ethyl acetate and heptane (1:2). This afforded 0.56 g (97%) of 3-{4-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]-pyridine-5-carbonyl]phenyl}acrylic acid tert butyl ester as an oil.

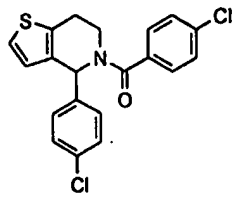
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.50 (9H, s), 2.8-3.1 (2H, m), 3.25 (1H, m), 3.65 (1H, m), 6.58 !1H, d), 6.78 (1H, bs), 6.87 (1H, d), 7.3-7.45 (7H, m), 7.60 (1H, d), 7.77 (2H, d).

The above tert-butyl ester (0.30 g, 0.62 mmol) was dissolved in dichloromethane (3 ml) and the mixture was cooled to 0 °C. At 0 °C trifluoroacetic acid (3 ml) was added and the mixture was stirred at 0 °C for 30 minutes. The mixture was concentrated in vacuo. The residue was dissolved in dichloromethane (5 ml), concentrated in vacuo dissolved again in methanol (5 ml) and concentrated in vacuo. 10.6 mg of the residue was dissolved in 750 µl methanol and purified by preparative HPLC using a Gilson binary gradient HPLC system equipped with 305 / 306 master/slave pumps, 117 UV detector and fraction collector. The eluting sample was detected at 210 and 225 nm. Flow rate was 15 ml/minute. The column was 20*250 mm ODS 10 µm (YMC) eluted with a gradient of acetonitrile (solvent B) and de-ionised water added 0.05% TFA (solvent A), 45%B to 100% B over 30 minutes. Fractions corresponding to T_R 12 - 14 minutes were pooled to yield 8.3 mg of the title compound.

MS: m/z 424 (M+1).

EXAMPLE 12:

(4-Chlorophenyl)-[4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No 22), less polar enantiomer



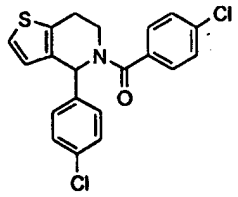
(4-Chlorophenyl)-[4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone (4.1 mg) was dissolved in a 1:2:4 mixture of ethyl acetate, heptane and 2-propanol (3.5 ml) and fractionated by HPLC using a 21.1 x 250 mm (*R,R*)-Whelk-O column (Regis). The column was eluted isocratically with a 1:1 mixture of heptane and 2-propanol at a flow rate of 10 ml/min and fractions collected corresponding to 1 min/fraction. The eluting enantiomers were detected spectroscopically by measuring absorbance at a wavelength of 225 nm. Two eluting peaks were detected, one corresponding to T_R 28-32 mininutes and one correspond-

ing to T_R 51-58 minutes. Fractions corresponding T_R 28-32 minutes were pooled and evaporated to yield 1.8 mg of the title compound.

100% ee (Determined by HPLC using a 4.6 x 250 mm (*R,R*)-Whelk-O column eluted with n-heptane:2-propanol (1:1), the flow rate was 1 ml/min, eluting sample was monitored spectroscopically at 225 nm, T_R 9.9 min)

EXAMPLE 13:

(4-Chlorophenyl)-[4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No 23), more polar enantiomer

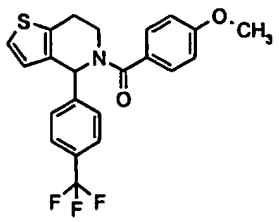


Fractions from example 12 corresponding to T_R 51-58 minutes were pooled and evaporated to yield 2.6 mg of the title compound.

99.5% ee (Conditions as described in example 12, T_R 15.5 min).

EXAMPLE 14:

[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 24), less polar enantiomer

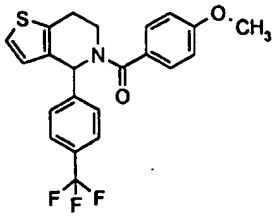


[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone (11.2 mg) was dissolved in a 1:1 mixture of heptane and 2-propanol (2 ml) and fractionated by HPLC using a 21.1 x 250 mm (*R,R*)-Whelk-O column (Regis). The column was eluted isocratically with a 1:1 mixture of heptane and 2-propanol at a flow rate of 10 ml/min and fractions collected corresponding to 1 minute/fraction. The eluting enantiomers were detected spectroscopically by measuring absorbance at a wavelength of 225 nm. Two eluting peaks were detected, one corresponding to T_R 40-43 minutes and one corresponding to T_R 55-59 minutes. Fractions corresponding to T_R 40-43 minutes were pooled and evaporated to yield 4.0 mg of the title compound.

>99% ee (Determined by HPLC using a 4.6 x 250 mm (*R,R*)-Whelk-O column eluted with a 1:1 mixture of heptane and 2-propanol, the flow rate was 1 ml/min, eluting sample was monitored spectroscopically at 225 and 245 nm, T_R 12.6 min).

EXAMPLE 15:

[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 25), more polar enantiomer

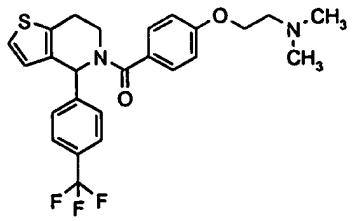


Fractions from example 14 corresponding to T_R 55-59 minutes were pooled and evaporated to yield 4.0 mg of the title compound.

99% ee (Conditions as described in example 14, T_R 16.4 min).

EXAMPLE 16:

[4-(2-Dimethylaminoethoxy)-phenyl]-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 26), less polar enantiomer

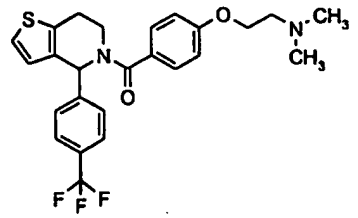


[4-(2-Dimethylaminoethoxy)-phenyl]-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone (*ca.* 20 mg) was dissolved in a 1:1 mixture of heptane and 2-propanol (1 ml) and fractionated by HPLC using a 20 x 250 mm Chiralcel OD column. The column was eluted isocratically with a 7:3:0.01 mixture of heptane, 2-propanol and diethylamine at a flow rate of 6 ml/min and fractions collected corresponding to 1 min/fraction. The eluting enantiomers were detected spectroscopically by measuring absorbance at a wavelength of 225 nm. Two eluting peaks were detected, one corresponding to T_R 20-25 minutes and one corresponding to T_R 27-33 minutes. Fractions corresponding to T_R 20-25 minutes were pooled and evaporated to yield 8.4 mg of the title compound.

>99.9% ee (Determined by HPLC using a 4.6 x 250 mm Chiralcel OD column eluted with a 70:30:0.07 mixture of heptane, 2-propanol and diethylamine, the flow rate was 0.4 ml/min, eluting sample was monitored spectroscopically at 225 and 245 nm, T_R 15.4 min).

EXAMPLE 17:

[4-(2-Dimethylaminoethoxy)-phenyl]-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 27), more polar enantiomer

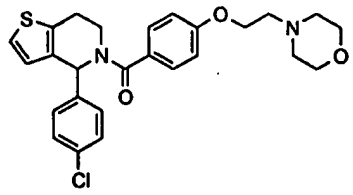


Fractions from example 16 corresponding to T_R 27-33 minutes were pooled and evaporated to yield 8.9 mg of the title compound.

>99% ee (Conditions as described in example 16, T_R 20.1 min).

EXAMPLE 18:

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-[4-(2-morpholin-4-ylethoxy)phenyl]-methanone, (compound No. 28), less polar enantiomer



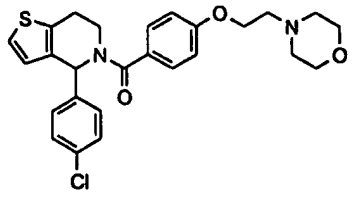
[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-[4-(2-morpholin-4-ylethoxy)phenyl]-methanone (*ca.* 10 mg) was dissolved in 3 ml a 15:15:1:0.2 mixture of heptane, 2-propanol, ethyl acetate and diethylamine (3 ml) and fractionated by HPLC using a 20 x 250 mm Chiralcel OD column. The column was eluted isocratically with a 70:30:0.1 mixture of heptane, 2-propanol and diethylamine at a flow rate of 6 ml/min and fractions col-

lected corresponding to 1 minute/fraction. The eluting enantiomers were detected spectroscopically by measuring absorbance at a wavelength of 225 nm. Two eluting peaks were detected, one corresponding to T_R 40-47 minutes and one corresponding to T_R 50-59 minutes. Fractions corresponding to T_R 40-47 minutes were pooled and evaporated to yield 4.1 mg of the title compound.

>99.9% ee (Determined by HPLC using a 4.6 x 250 mm Chiralcel OD column eluted with a 70:30:0.07 mixture of heptane, 2-propanol and diethylamine, the flow rate was 0.4 ml/min, eluting sample was monitored spectroscopically at 225 nm, T_R 22.9 min).

EXAMPLE 19:

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-[4-(2-morpholin-4-ylethoxy)phenyl]-methanone, (compound No. 29), more polar enantiomer

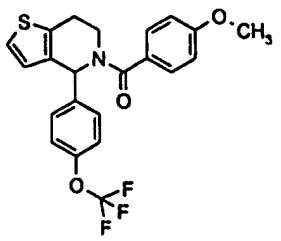


Fractions from example 18 corresponding to T_R 50-59 minutes were pooled and evaporated to yield 4.0 mg of the title compound.

98% ee (Conditions as described in example 18, T_R 28.5 min).

EXAMPLE 20:

[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 30), less polar enantiomer

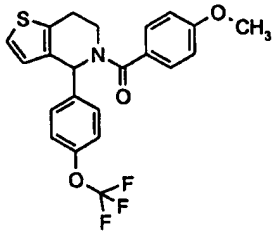


[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxy-phenyl)-methanone (10 mg) was dissolved in 2-propanol (0.5 ml) and fractionated by HPLC using a 21.1 x 250 mm (*R,R*)-Whelk-O column (Regis). The column was eluted isocratically with a 1:1 mixture of heptane and 2-propanol at a flow rate of 10 ml/min and fractions collected corresponding to 1 minute/fraction. The eluting enantiomers were detected spectroscopically by measuring absorbance at a wavelength of 225 nm. Two eluting peaks were detected, one corresponding to T_R 24-30 minutes and one corresponding to T_R 41-47 minutes. Fractions corresponding to T_R 24-30 minutes were pooled and evaporated to yield 2.5 mg of the title compound.

>99.8% ee (Determined by HPLC using a 4.6 x 250 mm (*R,R*)-Whelk-O column eluted with a 1:1 mixture of n-heptane and 2-propanol, the flow rate was 1 ml/minute, eluting sample was monitored spectroscopically at 225 and 254 nm, T_R 12.0 min)

EXAMPLE 21:

[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 31), more polar enantiomer



Fractions from example 20 corresponding to T_R 41-47 minutes were pooled and evaporated to yield 2.3 mg of the title compound.

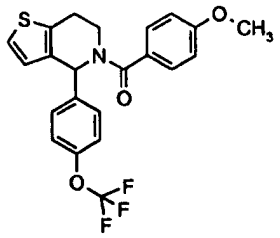
99.1% ee (Conditions as described in example 20, T_R 15.8 min).

The compounds of this invention can also be prepared by parallel syntheses, for example by a method essentially as described above, e.g. as described in example 3. The 1-hydroxybenzotriazole or another hydroxy azole known to be effective as alcohol component in active ester mediated amide coupling reactions can either be present in the reaction or it can be omitted depending on the substitution on the carboxylic acid part. This will be recognised by those skilled in the art.

A general procedure for parallel preparation of compounds of the invention is given in example 22:

EXAMPLE 22:

[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 32)



A solution of 4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) was added to a solution of 4-methoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol). To this solution 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) was added. The mixture was shaken overnight at

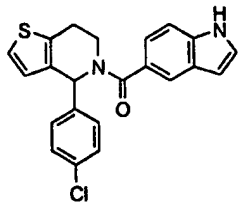
room temperature at 1000 rpm, added saturated NaCl (2 ml), and extracted with ethyl acetate (2 x 1 ml). The combined organic extracts were evaporated to afford the title compound.

MS (electrospray): m/z 434 (M+1)

HPLC (Method B): R_t = 33.2 min.

EXAMPLE 23:

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(1H-indol-5-yl)-methanone, (compound No. 33)



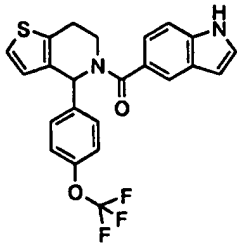
Similarly as described in example 22 using a solution of 4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of indole-5-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 393 (M+1)

HPLC (Method B): R_t = 30.7 min.

EXAMPLE 24:

(1H-Indol-5-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 34)



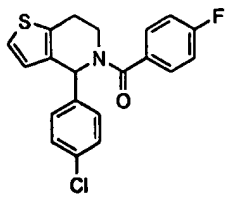
Similarly as described in example 22 using a solution of 4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of indole-5-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 443 (M+1)

HPLC (Method B): R_t = 31.5 min.

EXAMPLE 25:

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-fluorophenyl)-methanone, (compound No. 35)



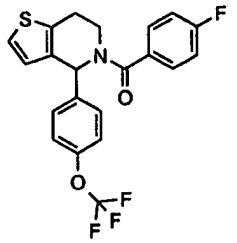
Similarly as described in example 22 using a solution of 4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-fluorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 372 (M+1)

HPLC (Method B): R_t = 32.6 min.

EXAMPLE 26:

[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-fluorophenyl)-methanone, (compound No. 36)



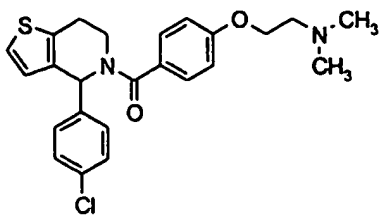
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-fluorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 422 (M+1)

HPLC (Method B): R_t = 32.2 min.

EXAMPLE 27:

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-[4-(2-dimethylaminoethoxy)phenyl]-methanone, (compound No. 37)



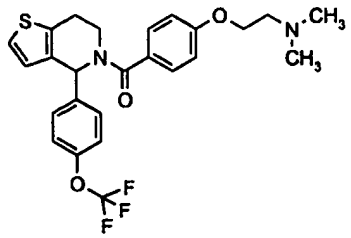
Similarly as described in example 22 using a solution of 4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a suspension of 4-(2-dimethylaminoethoxy)benzoic acid hydrochloride in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), triethylamine (42 µl), and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 441 (M+1)

HPLC (Method B): R_t = 23.4 min.

EXAMPLE 28:

[4-(2-Dimethylaminoethoxy)phenyl]-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 38)



Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a suspension of 4-(2-dimethylaminoethoxy)benzoic acid hydrochloride in N,N-dimethyl-formamide (0.375 M, 0.4 ml, 0.15 mmol), triethylamine (42 µl), and 0.25 ml of a suspension

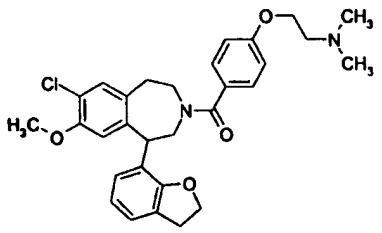
of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 491 (M+1)

HPLC (Method B): R_t = 24.9 min.

EXAMPLE 29:

[7-Chloro-1-(2,3-dihydrobenzofuran-7-yl)-8-methoxy-1,2,4,5-tetrahydrobenzo[d]azepin-3-yl]-[4-(2-dimethylaminoethoxy)-phenyl]-methanone, (compound No. 39)



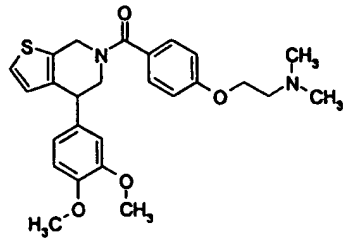
Similarly as described in example 22 using a solution of 7-chloro-1-(2,3-dihydrobenzofuran-7-yl)-8-methoxy-1,2,4,5-tetrahydrobenzo[d]azepine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a suspension of 4-(2-dimethylaminoethoxy)benzoic acid hydrochloride in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), triethylamine (42 µl), and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 521 (M+1)

HPLC (Method B): R_t = 22.9 min.

EXAMPLE 30:

[4-(3,4-Dimethoxyphenyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-6-yl]-[4-(2-dimethylaminoethoxy)-phenyl]-methanone, (compound No. 40)



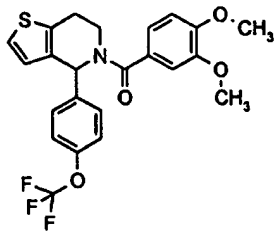
Similarly as described in example 22 using a solution of 4-(3,4-Dimethoxyphenyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a suspension of 4-(2-dimethylaminoethoxy)benzoic acid hydrochloride in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), triethylamine (42 µl), and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 467 (M+1)

HPLC (Method B): R_t = 18.1 min.

EXAMPLE 31:

(3,4-Dimethoxyphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 41)



Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3,4-dimethoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15

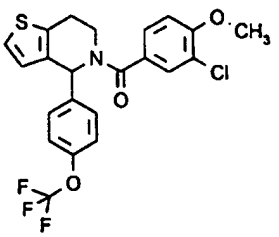
mmol), and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 464 (M+1)

HPLC (Method B): R_t = 32.1 min

EXAMPLE 32:

(3-Chloro-4-methoxyphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 42)



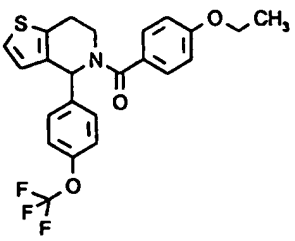
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-chloro-4-methoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 468 (M+1)

HPLC (Method B): R_t = 34.4 min

EXAMPLE 33:

(4-Ethoxyphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 43)

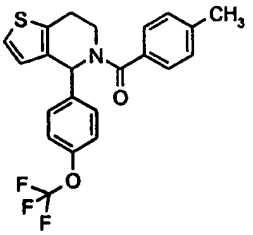


Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-ethoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 448 (M+1)
HPLC (Method B): R_t = 35.1 min

EXAMPLE 34:

(4-Methylphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 44)



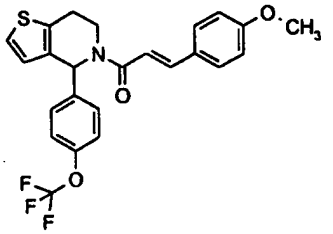
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 418 (M+1)

HPLC (Method B): R_t = 35.2 min

EXAMPLE 35:

3-(4-Methoxyphenyl)-1-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone, (compound No. 45)



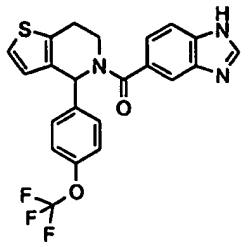
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxy-phenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxycinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 460 (M+1)

HPLC (Method B): R_t = 35.0 min

EXAMPLE 36:

(1H-Benzimidazol-5-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 46)

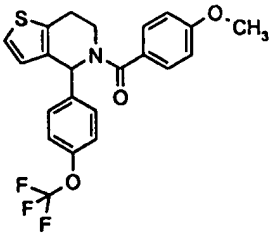


Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of benzimidazole-5-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z 444 (M+1)
HPLC (Method B): R_t = 23.1 min

EXAMPLE 37:

(4-Methoxyphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone



4-Methoxybenzoic acid (0.64 g, 4.2 mmol) was dissolved in N,N-dimethylformamide (25 ml) and 1-hydroxybenzotriazole (0.71 g, 5 mmol) was added followed by N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.96 g, 5 mmol). The resulting mixture was stirred at room temperature for 30 minutes. 4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (1.5 g, 5 mmol) followed by N,N-

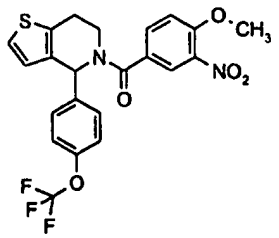
diisopropylethylamine (1.4 ml, 8.4 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. Water (10 ml) was added and the mixture was extracted with diethyl ether (3 x 20 ml). The combined organic extracts were washed with saturated aqueous ammonium chloride (20 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with a mixture of ethyl acetate and heptane (1:2). The pure fractions were pooled and concentrated *in vacuo*. The residue was crystallised from a mixture of methyl tert-butyl ether and heptane to afford 2.13 g (98%) of the title compound.

M.p. 68 - 70 °C.

Calculated for $C_{22}H_{18}F_3NO_3S.0.25H_2O$:
C, 60.34%; H, 4.26%; N, 3.20%. Found:
C, 60.35%; H, 4.38%; N, 3.07%;
C, 60.34%; H, 4.33%; N, 3.09%.

EXAMPLE 38:

[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone



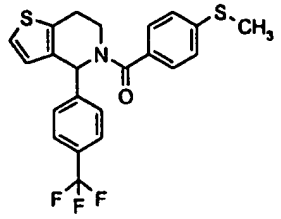
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxy-3-nitrobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/e: 479 (M+1)

HPLC (method B): R_t = 32.5 min.

EXAMPLE 39:

[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methylsulfanylphenyl)-methanone



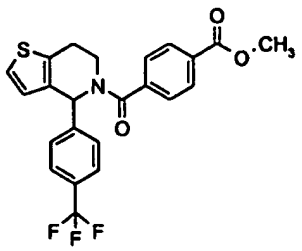
Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methylsulfanylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 434 (M+1)

HPLC (method B): R_t = 33.5 min.

EXAMPLE 40:

4-[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]benzoic acid methyl ester



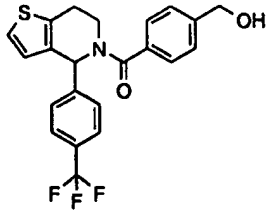
Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of mono methyl terephthalic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 446 (M+1)

HPLC (method B): R_t = 31.9 min.

EXAMPLE 41:

(4-Hydroxymethylphenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone



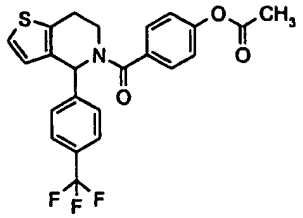
Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-hydroxymethylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 418 (M+1)

HPLC (method B): R_t = 27.2 min.

EXAMPLE 42:

(4-Acetoxyphenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone



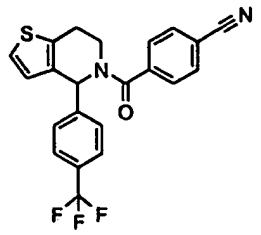
Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-acetoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 446 (M+1)

HPLC (method B): R_t = 30.7 min.

EXAMPLE 43:

(4-Cyanophenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

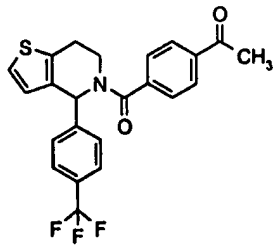


Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-cyanobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 413 (M+1)
HPLC (method B): R_t = 30.6 min.

EXAMPLE 44:

1-{4-[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]phenyl}ethanone



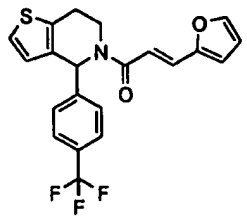
Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-acetylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 430 (M+1)

HPLC (method B): R_t = 30.5 min.

EXAMPLE 45:

3-Furan-2-yl-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone



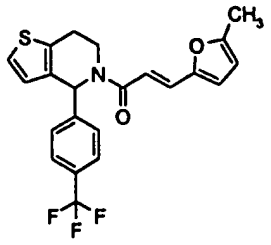
Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-(furan-2-yl)acrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 404 (M+1)

HPLC (method B): R_t = 32.2 min.

EXAMPLE 46:

3-(5-Methylfuran-2-yl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone

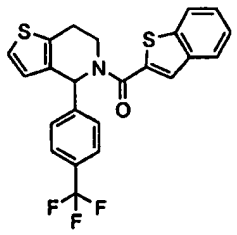


Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-(5-methylfuran-2-yl)acrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 418 (M+1)
HPLC (method B): R_t = 33.7 min.

EXAMPLE 47:

Benzo[b]thiophen-2-yl-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone



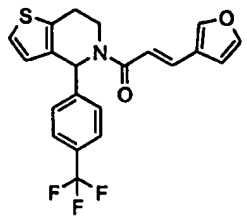
Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of benzo[b]thiophen-2-yl-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 444 (M+1)

HPLC (method B): R_t = 35.1 min.

EXAMPLE 48:

3-Furan-3-yl-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone



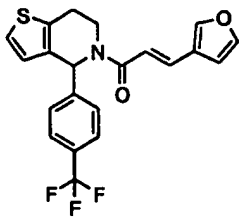
Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-furan-3-ylacrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 404 (M+1)

HPLC (method B): R_t = 31.4 min.

EXAMPLE 49:

3-Thiophen-3-yl-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone

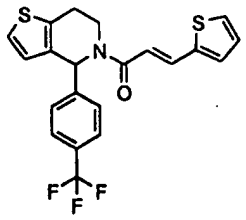


Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-thiophen-3-ylacrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 420 (M+1)
HPLC (method B): R_t = 32.8 min.

EXAMPLE 50:

3-Thiophen-2-yl-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone



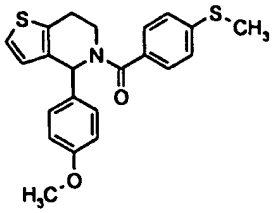
Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-thiophen-3-ylacrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 420 (M+1)

HPLC (method B): R_t = 33.3 min.

EXAMPLE 51:

[4-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methylsulfanylphenyl)methanone



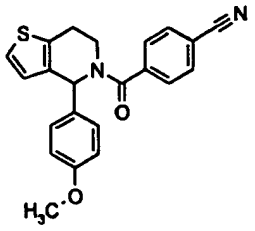
Similarly as described in example 22 using a solution of 4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methylsulfanylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 396 (M+1)

HPLC (method B): R_t = 29.5 min.

EXAMPLE 52:

4-[4-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]benzonitrile



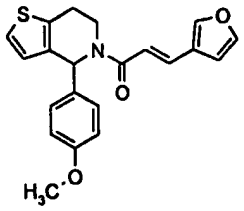
Similarly as described in example 22 using a solution of 4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-cyanobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 375 (M+1)

HPLC (method B): R_t = 26.2 min.

EXAMPLE 53:

3-Furan-3-yl-1-[4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone



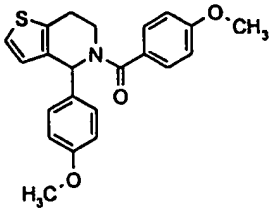
Similarly as described in example 22 using a solution of 4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-(furan-3-yl)acrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 366 (M+1)

HPLC (method B): R_t = 26.9 min.

EXAMPLE 54:

(4-Methoxyphenyl)-[4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone



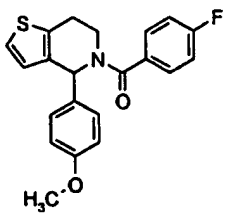
Similarly as described in example 22 using a solution of 4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 380 (M+1)

HPLC (method B): R_t = 27.6 min.

EXAMPLE 55:

(4-Fluorophenyl)-[4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone



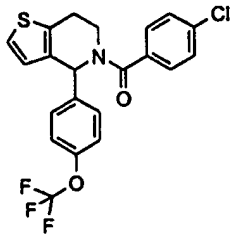
Similarly as described in example 22 using a solution of 4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-fluorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 368 (M+1)

HPLC (method B): R_t = 27.7 min.

EXAMPLE 56:

(4-Chlorophenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone



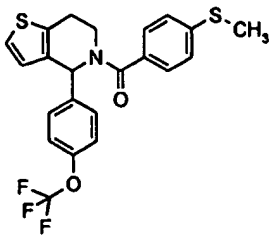
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-chlorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 438 (M+1)

HPLC (method B): R_t = 32.8 min.

EXAMPLE 57:

(4-Methylsulfanylphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone



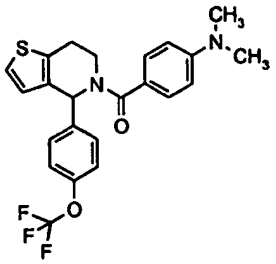
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methylsulfanylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 450 (M+1)

HPLC (method B): R_t = 32.6 min.

EXAMPLE 58:

(4-Dimethylaminophenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

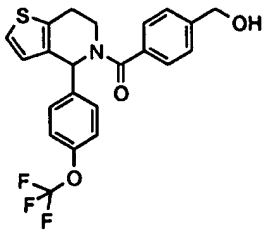


Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-dimethylaminobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 447 (M+1)
HPLC (method B): R_t = 27.1 min.

EXAMPLE 59:

(4-Hydroxymethylphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

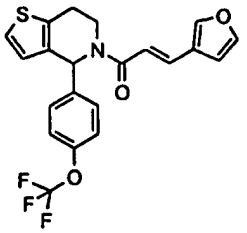


Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-hydroxymethylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 434 (M+1)
HPLC (method B): R_t = 26.6 min.

EXAMPLE 60:

3-Furan-3-yl-1-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone



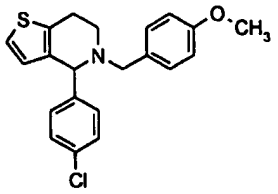
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-(3-furan-3-yl)acrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 420 (M+1)

HPLC (method B): R_t = 30.4 min.

EXAMPLE 61:

4-(4-Chlorophenyl)-5-(4-methoxybenzyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine hydrochloride



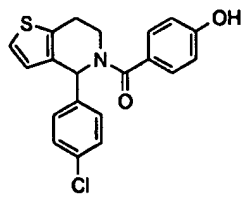
4-(4-Chlorophenyl)- 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (0.10 g, 0.38 mmol) was dissolved in N,N-dimethylformamide (0.5 ml) and triethylamine (110 µl, 0.76 mmol) and 4-methoxybenzyl chloride (51 µl, 0.38 mmol) were added and the resulting mixture was

shaken at 1000 rpm for 3 days. Water (2 ml) was added and the mixture was extracted with ethyl acetate (2 x 1 ml). The combined organic extracts were concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography eluting with a mixture of ethyl acetate and heptane (1:4) to afford the free base. This was dissolved in diethyl ether and 1N HCl in diethyl ether was added drop wise to complete precipitation to afford 52 mg (34%) of the title compound.

HPLC-MS: R_t = 9.57 min. m/z = 370 (M+1).

EXAMPLE 62:

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-hydroxyphenyl)methanone



4-Hydroxybenzoic acid (1.3 g, 9.6 mmol) was dissolved in N,N-dimethylformamide (25 ml) and 1-hydroxybenzotriazole (1.3 g, 9.6 mmol) was added followed by N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.8 g, 9.6 mmol), 4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine (2.0 g, 8 mmol) and N,N-diisopropylethylamine (2.5 ml, 16 mmol). The resulting mixture was stirred at room temperature for 16 hours. Water (200 ml) was added and the mixture was extracted with diethyl ether (3 x 100 ml). The combined organic extracts were washed with saturated aqueous sodium chloride (150 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with a mixture of ethyl acetate and heptane (1:1). The pure fractions were pooled and concentrated *in vacuo* to afford 3.14 g (100%) of the title compound.

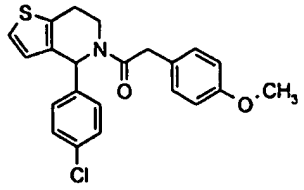
M.p. 202 - 207 °C.

Calculated for $C_{20}H_{16}ClNO_2S$:
C, 64.95%; H, 4.36%; N, 3.79%. Found:
C, 64.54%; H, 4.74%; N, 4.29%;
C, 64.63%; H, 4.76%; N, 4.28%.

HPLC-MS: R_t = 14.18 min. m/z: 370 (M+1)

EXAMPLE 63:

1-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-2-(4-methoxyphenyl)ethanone

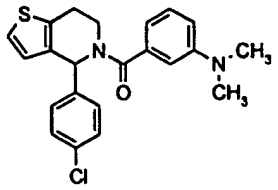


Similarly as described in example 22 using a solution of 4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxyphenylacetic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 398 (M+1)
HPLC (method B): R_t = 32.2 min.

EXAMPLE 64:

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(3-dimethylaminophenyl)methanone



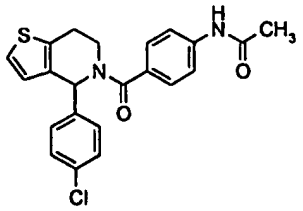
Similarly as described in example 22 using a solution of 4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-dimethylaminobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 397 (M+1)

HPLC (method B): R_t = 25.9 min.

EXAMPLE 65:

N-{4-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]-phenyl}acetamide



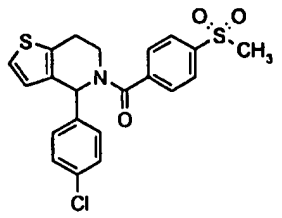
Similarly as described in example 22 using a solution of 4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-acetamidobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 411 (M+1)

HPLC (method B): R_t = 27.2 min.

EXAMPLE 66:

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methanesulfonylphenyl)methanone



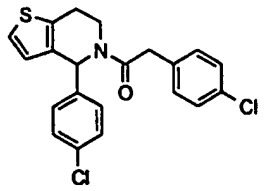
Similarly as described in example 22 using a solution of 4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methanesulfonylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 432 (M+1)

HPLC (method B): R_t = 28.1 min.

EXAMPLE 67:

2-(4-Chlorophenyl)-1-[4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]ethanone

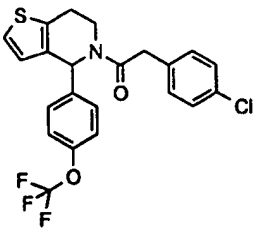


Similarly as described in example 22 using a solution of 4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-chlorophenylacetic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 402 (M+1)
HPLC (method B): R_t = 34.5 min.

EXAMPLE 68:

2-(4-Methoxyphenyl)-1-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone



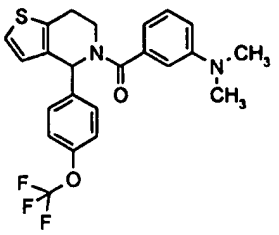
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-chlorophenylacetic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 448 (M+1)

HPLC (method B): R_t = 32.9 min.

EXAMPLE 69:

(3-Dimethylaminophenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone



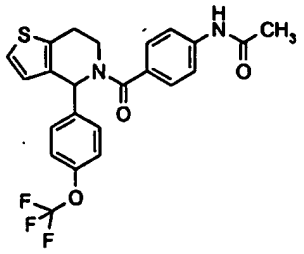
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-dimethylaminobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 447 (M+1)

HPLC (method B): R_t = 27.2 min.

EXAMPLE 70:

N-{4-[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]-phenyl}-acetamide

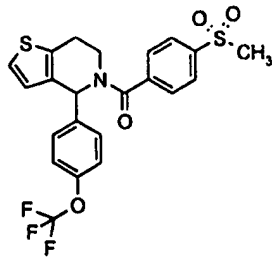


Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-acetamidobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 461 (M+1)
HPLC (method B): R_t = 28.2 min.

EXAMPLE 71:

(4-Methanesulfonylphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone



Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methanesulfonylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15

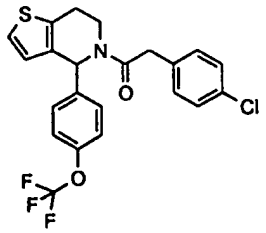
mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 482 (M+1)

HPLC (method B): R_t = 29.1 min.

EXAMPLE 72:

2-(4-Chlorophenyl)-1-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-ethanone



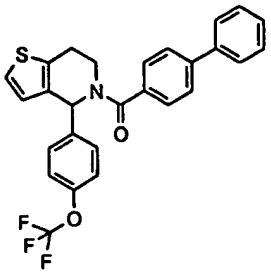
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-chlorophenylacetic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 452 (M+1)

HPLC (method B): R_t = 34.9 min.

EXAMPLE 73:

Biphenyl-4-yl-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone



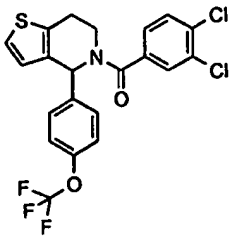
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-biphenylcarboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 480 (M+1)

HPLC (method B): R_t = 36.7 min.

EXAMPLE 74:

(3,4-Dichlorophenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone



Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3,4-dichlorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol)

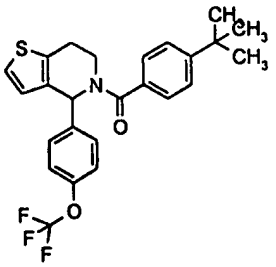
and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 472 (M+1)

HPLC (method B): R_t = 36.2 min.

EXAMPLE 75:

(4-tert-Butylphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone



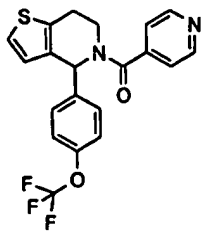
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-tert-butylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 460 (M+1)

HPLC (method B): R_t = 37.0 min.

EXAMPLE 76:

Pyridin-4-yl-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone



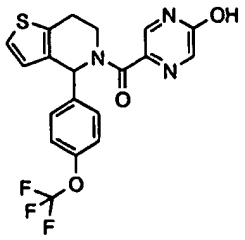
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of pyridine-4-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 405 (M+1)

HPLC (method B): R_t = 23.9 min.

EXAMPLE 77:

(5-Hydroxypyrazin-2-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone



Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 5-hydroxypyrazine-2-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml,

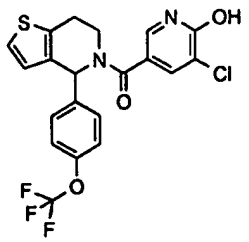
0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 422 (M+1)

HPLC (method B): R_t = 26.0 min.

EXAMPLE 78:

(5-Chloro-6-hydroxypyridin-3-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone



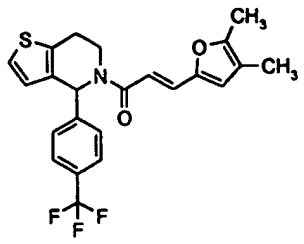
Similarly as described in example 22 using a solution of 4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 2-hydroxy-3-chloropyridine-5-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 455 (M+1)

HPLC (method B): R_t = 26.8 min.

EXAMPLE 79:

3-(4,5-Dimethylfuran-2-yl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone



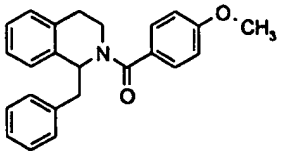
Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-(4,5-dimethylfuran-2-yl)acrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

MS (electrospray): m/z: 432 (M+1)

HPLC (method B): R_t = 35.2 min.

EXAMPLE 80:

(1-Benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)-(4-methoxyphenyl)methanone

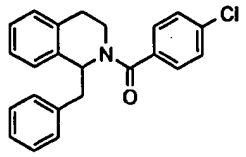


Similarly as described in example 22 using a solution of 1-benzyl-1,2,3,4-tetrahydro-isoquinoline in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 15.0 min. m/z: 358 (M+1)

EXAMPLE 81:

(1-Benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)-(4-chlorophenyl)methanone

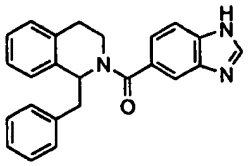


Similarly as described in example 22 using a solution of 1-benzyl-1,2,3,4-tetrahydro-isoquinoline in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-chlorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in di-chloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 16.1 min. m/z: 362 (M+1)

EXAMPLE 82:

(1H-Benzoimidazol-5-yl)-(1-benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)methanone

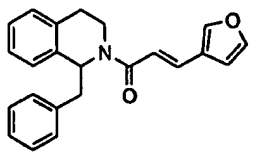


Similarly as described in example 22 using a solution of 1-benzyl-1,2,3,4-tetrahydro-isoquinoline in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of benzimidazole-5-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 9.55 min. m/z: 368 (M+1)

EXAMPLE 83:

1-(1-Benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)-3-furan-3-ylpropenone

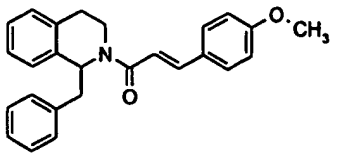


Similarly as described in example 22 using a solution of 1-benzyl-1,2,3,4-tetrahydro-isoquinoline in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-(3-furan-3-yl)acrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 14.7 min. m/z: 344 (M+1)

EXAMPLE 84:

1-(1-Benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)-3-(4-methoxyphenyl)propenone

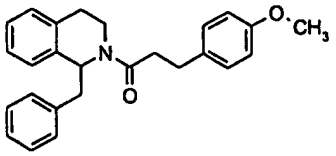


Similarly as described in example 22 using a solution of 1-benzyl-1,2,3,4-tetrahydro-isoquinoline in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxycinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 15.7 min. m/z: 384 (M+1)

EXAMPLE 85:

1-(1-Benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)-3-(4-methoxyphenyl)propan-1-one

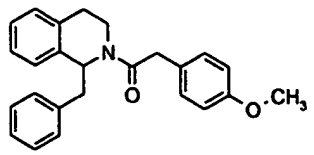


Similarly as described in example 22 using a solution of 1-benzyl-1,2,3,4-tetrahydro-isoquinoline in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxyhydrocinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 15.7 min. m/z: 386 (M+1)

EXAMPLE 86:

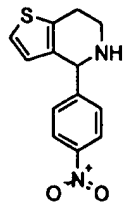
1-(1-Benzyl-1,2,3,4-tetrahydro-isoquinolin-2-yl)-2-(4-methoxyphenyl)ethanone



Similarly as described in example 22 using a solution of 1-benzyl-1,2,3,4-tetrahydro-isoquinoline in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxyphenylacetic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 15.2 min. m/z: 372 (M+1)

Preparation of 4-(4-nitro-phenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine trifluoroacetate:



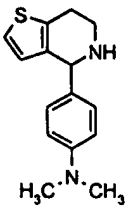
2-(2-Thienyl)-ethylamine (5 g, 39.4 mmol), 4-nitrobenzaldehyde and triethylamine (10 ml) were dissolved in ethanol (100 ml). The reaction mixture was stirred at room temperature for 48 hours. The solid formed was filtered and dried to afford 7.75 g (76%) *(4-nitrobenzylidene)-(2-thiophen-2-yl-ethyl)-amine.*

M.p.: 83.9-84.4 °C.

The above (4-nitrobenzylidene)-(2-thiophen-2-yl-ethyl)-amine (1 g, 3.8 mmol) was added trifluoroacetic acid (100 ml) at once (strongly exothermic reaction). The reaction mixture was stirred at room temperature for 72 hours, then evaporated *in vacuo*. Crystallisation from a mixture of diethyl ether and dichloromethane afforded 1.2 g (85%) of the title compound.

M.p.: 128-129.5 °C.

Preparation of dimethyl-[4-(4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-4-yl)-phenyl]-amine:



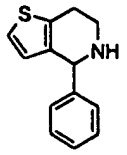
2-(2-Thienyl)-ethylamine (5 g, 39.4 mmol), 4-dimethylaminobenzaldehyde (5.9 g, 94 mmol) triethylamine (6 ml) and ethanol (150ml) were mixed at room temperature. The reaction mixture was stirred at room temperature for 15 hours. The reaction mixture was concentrated to 75 ml by evaporation *in vacuo* and the solid formed was filtered and dried to afford 6.82 g (67%) *dimethyl-{4-[(2-thiophen-2-yl-ethylimino)-methyl]-phenyl}-amine*.

M.p.: 76.8-77 °C.

The above dimethyl-{4-[(2-thiophen-2-yl-ethylimino)-methyl]-phenyl}-amine (1 g, 3.9 mmol) was added TFA (20 mL) at once (strongly exothermic reaction). The reaction mixture was stirred at room temperature for 72 hours, then evaporated *in vacuo*. The crude oil was suspended in dichloromethane (75 ml) and extracted with 1 N hydrochloric acid (50 ml). The aqueous phase was added 2 N sodium hydroxide to pH=10, then extracted with dichloromethane (3x125 ml). The organic phase was dried with $MgSO_4$, filtered, evaporated *in vacuo* to afford 0.96 g (95%) of the title compound.

M.p.: 95-98 °C.

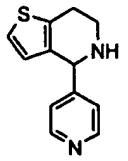
Preparation of 4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine:



2-(2-Thienyl)-ethylamine (2 g, 15.7 mmol) and benzaldehyde (1.67 g, 15.7 mmol) were dissolved in toluene (50 ml) and the reaction mixture was heated at reflux until 20 ml of toluene and water was distilled of in a Dean Stark trap. The remaining mixture was evaporated *in vacuo* to give the crude imine (3.44 g). The crude imine was added trifluoroacetic acid (50 ml) at once (strongly exothermic reaction). The reaction mixture was stirred at room temperature for 72 hours, then evaporated *in vacuo*. The crude oil was dissolved in dichloromethane (50 ml) and washed with 2 N sodium hydroxide (30 ml). The aqueous phase was extracted with dichloromethane (3x30ml). The combined organic phases were dried with $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with a mixture of dichloromethane and methanol (19:1). This afforded 0.823 g (24%) of the title compound.

M.p.: 79.8-80.7 °C

Preparation of 4-(pyridin-4-yl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine, NNC 60-0372.

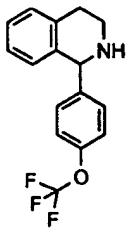


2-(2-Thienyl)-ethylamine (2 g, 15.7 mmol) 4-pyridylaldehyde (1.68 g, 15.7 mmol), triethylamine (1 ml) and ethanol (15 ml) were mixed and the reaction mixture was stirred at room temperature for 15 hours, then evaporated *in vacuo*. The crude oil was added trifluoroacetic acid (75 m) at once (strongly exothermic reaction). The reaction mixture was stirred at room temperature for 0.5 hour, then evaporated *in vacuo*. The residue was dissolved in dichloromethane (150 ml) and washed with 2 N sodium hydroxide (100 ml). The aqueous phase was extracted with dichloromethane (3 x 50 ml). The combined organic phases were

dried with $MgSO_4$, filtered and evaporated *in vacuo* to give an oil (3.21 g) which was crystallised from a mixture of dichloromethane and hexane to afford 2.4 g (71%) of the title compound.

M.p.: 81.8-83.8 °C.

Preparation of 1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydro-isoquinoline:



Phenethylamine (0.59 g, 4.9 mmol), 4-trifluoromethoxybenzoic acid (1.0 g, 4.9 mmol) and N-(3-dimethylaminopropyl)-N-ethylcarbodimide, HCl (1.39 g, 7.3 mmol) were mixed in N,N-dimethylformamide (50 mL) at room temperature and the reaction mixture was stirred for 16 hours. Water (50 mL) was added and the mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo* giving 1.5 g crude product which was purified by column chromatography on silica gel eluting with a mixture of dichloromethane and methanol (9:1). This afforded 0.67 g (45%) of N-phenethyl-4-trifluoromethoxybenzamide.

M.p.: 143.2-143.9 °C.

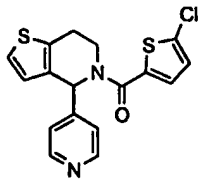
The above N-phenethyl-4-trifluoromethoxybenzamide (0.67 g, 2.2 mmol) was added to a mixture of phosphorous pentoxide (0.92 g, 6.5 mmol) and phosphorous oxychloride (1.03 g, 6.7 mmol) in xylene (50 mL). The reaction mixture was stirred at 140 °C for 16 hours. After cooling, water (50 mL) was added and the mixture was basified with 1 N NaOH. The aqueous phase was extracted with xylene (3 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo* giving 0.96 g crude product which was purified by column chromatography on silica gel eluting with a mixture of dichloromethane and methanol (9:1). This afforded 0.40 g (62%) of 1-(4-Trifluoromethoxy-phenyl)-3,4-dihydro-isoquinoline as an oil.

The above 1-(4-trifluoromethoxyphenyl)-3,4-dihydro-isoquinoline (0.40 g, 1.4 mmol) was dissolved in methanol (20 mL) and sodium borohydride (0.08 g, 2.1 mmol) was added slowly. The reaction mixture was stirred at room temperature for 2.5 hours. The mixture was evaporated *in vacuo*, redissolved in 1 N NaOH (20 mL) and extracted with dichloromethane (50 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The remaining oil (0.35 g) was purified by column chromatography on silica gel eluting with a mixture of dichloromethane and methanol (9:1). This afforded 0.56 g (56%) of the title compound.

M.p.: 56.6- 57.1 °C.

EXAMPLE 87:

(5-Chlorothiophen-2-yl)-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)methanone

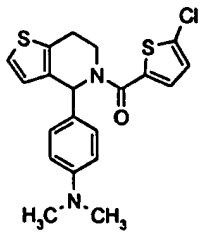


Similarly as described in example 22 using a solution of 4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 5-chlorothiophene-2-carboxylic acid acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 9.27 min. m/z: 361 (M+1)

EXAMPLE 88:

(5-Chlorothiophen-2-yl)-[4-(4-dimethylaminophenyl)4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

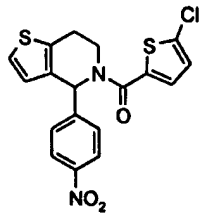


Similarly as described in example 22 using a solution of 4-dimethylaminophenyl)4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 5-chlorothiophene-2-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 10.70 min. m/z: 403 (M+1)

EXAMPLE 89:

(5-Chlorothiophen-2-yl)-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)methanone



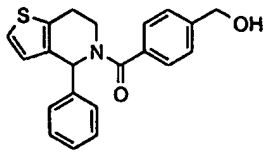
Similarly as described in example 22 using a solution of 4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 5-chlorothiophene-2-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol)

and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 16.18 min. m/z: 405 (M+1)

EXAMPLE 90:

(4-Hydroxymethylphenyl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)methanone

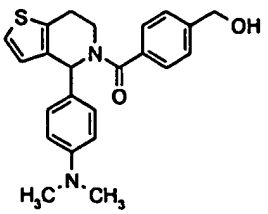


Similarly as described in example 22 using a solution of 4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-hydroxymethylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 12.33 min. m/z: 350 (M+1)

EXAMPLE 91:

[4-(4-Dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-(4-hydroxymethylphenyl)-methanone

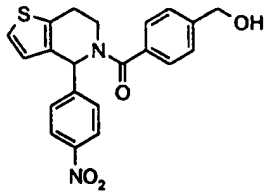


Similarly as described in example 22 using a solution of 4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-hydroxymethylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 8.07 min. m/z: 393 (M+1)

EXAMPLE 92:

[4-(4-Nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-(4-hydroxymethylphenyl)-methanone

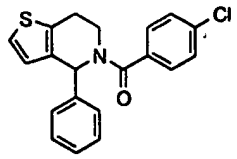


Similarly as described in example 22 using a solution of 4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-hydroxymethylbenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 12.44 min. m/z: 395 (M+1)

EXAMPLE 93:

(4-Chlorophenyl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)methanone

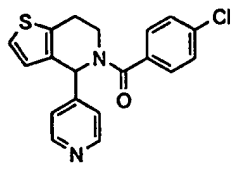


Similarly as described in example 22 using a solution of 4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-chlorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in di-chloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 15.90 min. m/z: 355 (M+1)

EXAMPLE 94:

(4-Chlorophenyl)-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone



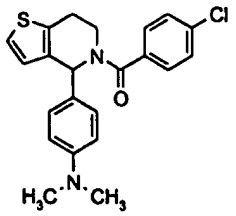
Similarly as described in example 22 using a solution of 4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-

chlorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 9.18 min. m/z: 355 (M+1)

EXAMPLE 95:

(4-Chlorophenyl)-[4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

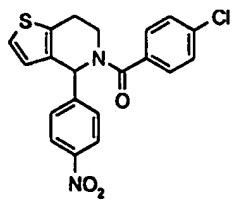


Similarly as described in example 22 using a solution of 4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-chlorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 10.43 min. m/z: 397 (M+1)

EXAMPLE 96:

(4-Chlorophenyl)-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

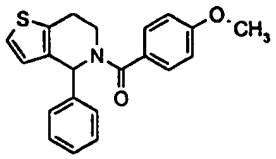


Similarly as described in example 22 using a solution of 4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-chlorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 15.81 min. m/z: 399 (M+1)

EXAMPLE 97:

(4-Methoxyphenyl)-[4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

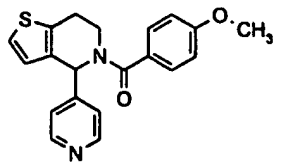


Similarly as described in example 22 using a solution of 4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 14.83 min. m/z: 350 (M+1)

EXAMPLE 98:

(4-Methoxyphenyl)-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

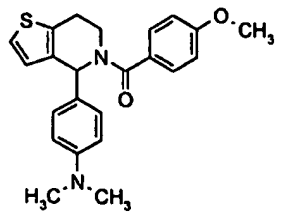


Similarly as described in example 22 using a solution of 4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 8.50 min. m/z: 351 (M+1)

EXAMPLE 99:

[4-(4-Dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone



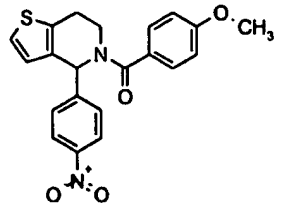
Similarly as described in example 22 using a solution of 4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-

methoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 9.55 min. m/z: 393 (M+1)

EXAMPLE 100:

[4-(4-Dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone

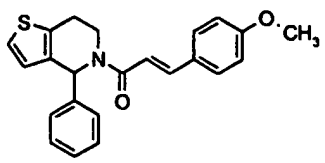


Similarly as described in example 22 using a solution of 4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 14.80 min. m/z: 395 (M+1)

EXAMPLE 101:

3-(4-Methoxyphenyl)-1-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-propenone

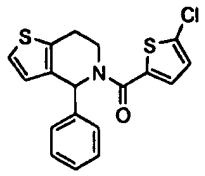


Similarly as described in example 22 using a solution of 4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxycinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 15.45 min. m/z: 376 (M+1)

EXAMPLE 102:

(5-Chlorothiophen-2-yl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

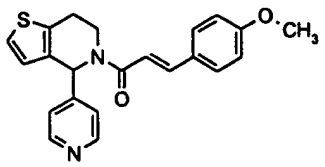


Similarly as described in example 22 using a solution of 4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 5-chlorothiophene-2-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 16.42 min. m/z: 360 (M+1)

EXAMPLE 103:

3-(4-Methoxyphenyl)-1-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-propenone

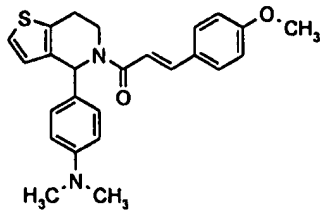


Similarly as described in example 22 using a solution of 4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxycinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 9.42 min. m/z: 377 (M+1)

EXAMPLE 104:

1-[4-(4-Dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-3-(4-methoxyphenyl)-propenone



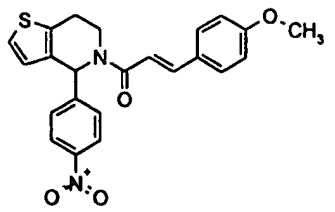
Similarly as described in example 22 using a solution of 4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a

solution of 4-methoxycinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 10.32 min. m/z: 418 (M+1)

EXAMPLE 105:

3-(4-Methoxyphenyl)-1-(4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-propenone

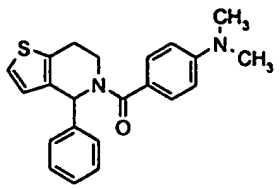


Similarly as described in example 22 using a solution of 4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxycinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 15.47 min. m/z: 421 (M+1)

EXAMPLE 106:

(4-Dimethylaminophenyl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

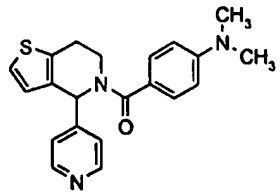


Similarly as described in example 22 using a solution of 4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-dimethylaminobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 11.83 min. m/z: 363 (M+1)

EXAMPLE 107:

(4-Dimethylaminophenyl)-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

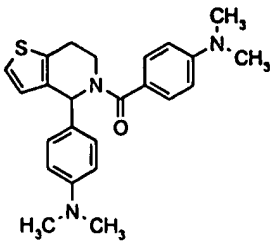


Similarly as described in example 22 using a solution of 4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-dimethylaminobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 7.5 min. m/z: 364 (M+1)

EXAMPLE 108:

(4-Dimethylaminophenyl)-[4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone

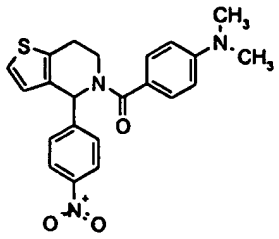


Similarly as described in example 22 using a solution of 4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-dimethylaminobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 8.15 min. m/z: 406 (M+1)

EXAMPLE 109:

(4-Dimethylaminophenyl)-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone

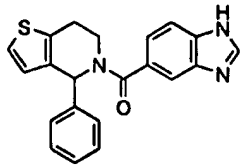


Similarly as described in example 22 using a solution of 4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-dimethylaminobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 12.68 min. m/z: 408 (M+1)

EXAMPLE 110:

(1H-Benzoimidazol-5-yl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

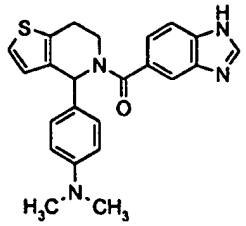


Similarly as described in example 22 using a solution of 4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of benzimidazole-5-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 9.27 min. m/z: 360 (M+1)

EXAMPLE 111:

(1H-Benzoimidazol-5-yl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

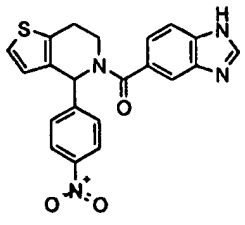


Similarly as described in example 22 using a solution of 4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of benzimidazole-5-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 7.17 min. m/z: 403 (M+1)

EXAMPLE 112:

(1H-Benzoimidazol-5-yl)-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone

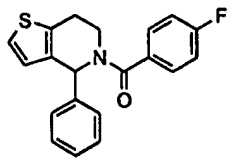


Similarly as described in example 22 using a solution of 4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of benzimidazole-5-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 9.50 min. m/z: 405 (M+1)

EXAMPLE 113:

(4-Fluorophenyl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

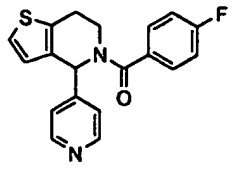


Similarly as described in example 22 using a solution of 4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-fluorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 15.07 min. m/z: 339 (M+1)

EXAMPLE 114:

(4-Fluorophenyl)-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

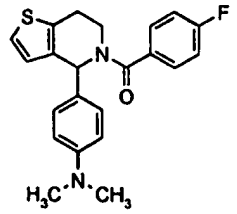


Similarly as described in example 22 using a solution of 4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-fluorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 8.62 min. m/z: 339 (M+1)

EXAMPLE 115:

[4-(4-Dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-fluorophenyl)-methanone

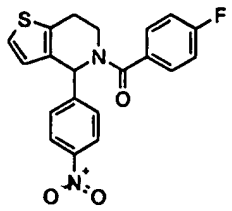


Similarly as described in example 22 using a solution of 4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-fluorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 9.68 min. m/z: 381 (M+1)

EXAMPLE 116:

(4-Fluorophenyl)-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone

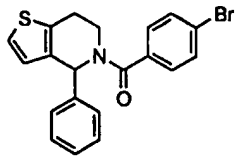


Similarly as described in example 22 using a solution of 4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-fluorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 14.95 min. m/z: 383 (M+1)

EXAMPLE 117:

(4-Bromophenyl)-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone



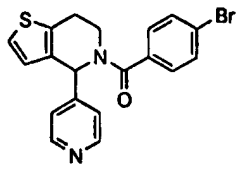
Similarly as described in example 22 using a solution of 4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-

bromobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 16.07 min. m/z: 398 + 400 (M+1)

EXAMPLE 118:

(4-Bromophenyl)-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

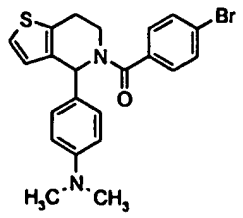


Similarly as described in example 22 using a solution of 4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-bromobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 9.30 min. m/z: 399 + 401 (M+1)

EXAMPLE 119:

(4-Bromophenyl)-[4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone

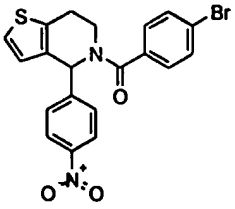


Similarly as described in example 22 using a solution of 4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-bromobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 10.72 min. m/z: 441 + 443 (M+1)

EXAMPLE 120:

(4-Bromophenyl)-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone

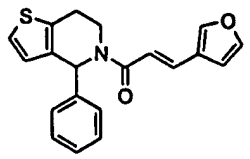


Similarly as described in example 22 using a solution of 4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-bromobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 15.84 min. m/z: 442 + 444 (M+1)

EXAMPLE 121:

3-Furan-3-yl-1-(4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-propenone

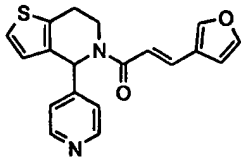


Similarly as described in example 22 using a solution of 4-phenyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-furan-3-ylacrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 14.77 min. m/z: 336 (M+1)

EXAMPLE 122:

3-(3-Furan-3-yl)-1-(4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-propenone



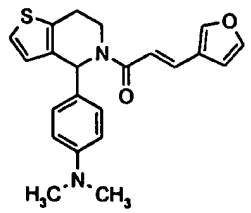
Similarly as described in example 22 using a solution of 4-pyridin-4-yl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-furan-3-ylacrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of

a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 8.58 min. m/z: 337 (M+1)

EXAMPLE 123:

1-[4-(4-Dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-3-(3-furan-3-yl)-propenone

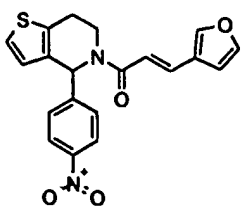


Similarly as described in example 22 using a solution of 4-(4-dimethylaminophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-furan-3-ylacrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 9.38 min. m/z: 379 (M+1)

EXAMPLE 124:

3-(3-Furan-3-yl)-1-[4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-propenone

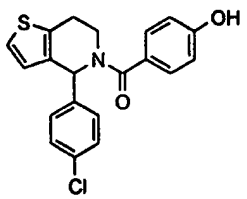


Similarly as described in example 22 using a solution of 4-(4-nitrophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-furan-3-ylacrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 14.57 min. m/z: 381 (M+1)

EXAMPLE 125:

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-hydroxyphenyl)-methanone, less polar enantiomer,



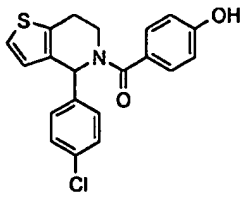
[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-hydroxyphenyl)-methanone (21 mg) was dissolved in a 1:1:1 mixture of ethyl acetate, 2-propanol and n-heptane (3 ml) and fractionated by HPLC using a 21.1 x 250 mm (*R,R*)-Whelk-O column (Regis). The column was eluted isocratically with a mixture of n-heptane and 2-propanol (1:1) at a flow rate of 10 ml/min and fractions were collected corresponding to 1 min/fraction. The eluting enantiomers were detected spectroscopically by measuring absorbance at a wavelength of 225 nm. Two eluting peaks were detected, corresponding to T_R 24-29 minutes

and T_R 42-50 minutes, respectively. Fractions corresponding to T_R 24-29 minutes were pooled and evaporated to yield 8.8 mg of the title compound.

100% ee (Determined by HPLC using a 4.6 x 250 mm (*R,R*)-Whelk-O column eluted with n-heptane:2-propanol (1:1), the flow rate was 1 ml/min, eluting sample was monitored spectroscopically at 225 and 280 nm, T_R 8.9 min).

EXAMPLE 126:

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-hydroxyphenyl)-methanone, more polar enantiomer,

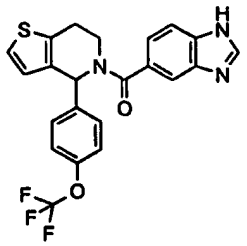


Fractions from example 125 corresponding to T_R 42-50 minutes were pooled and evaporated to yield 9.1 mg of the title compound.

99.4 % ee (Conditions as described in example 125, T_R 12.5 min).

EXAMPLE 127:

(1H-Benzoimidazol-5-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, less polar enantiomer,

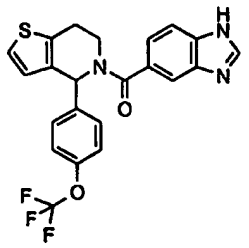


(1H-Benzoimidazol-5-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone (15 mg) was dissolved in a 1:1 mixture of n-heptane:2-propanol (2 ml) and fractionated by HPLC using a 20 x 250 mm Chiralpak AS column. The column was eluted isocratically with a mixture of n-heptane, ethanol and diethylamine (70:30:0.1) at a flow rate of 6 ml/min and fractions collected corresponding to 1 min/fraction. The eluting enantiomers were detected spectroscopically by measuring absorbance at a wavelength of 225 nm. Two eluting peaks were detected, corresponding to T_R 16-19 minutes and T_R 27-35 minutes, respectively. Fractions corresponding to T_R 16-19 minutes were pooled and evaporated to yield 7.2 mg of the title compound.

100% ee (Determined by HPLC using a 4.6 x 250 mm Chiralpak AS column eluted with a mixture of n-heptane, ethanol and diethylamine (70:30:0.07), the flow rate was 0.6 ml/min, eluting sample was monitored spectroscopically at 225 and 245 nm, T_R 8.4 min).

EXAMPLE 128:

(1H-Benzoimidazol-5-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, more polar enantiomer,

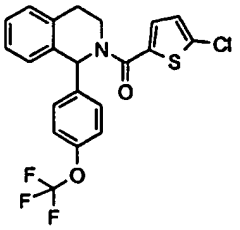


Fractions from example 127 corresponding to T_R 27-35 minutes were pooled and evaporated to yield 8.0 mg of the title compound.

>99% ee (Conditions as described in example 127, T_R 14.7 min).

EXAMPLE 129:

(5-Chlorothiophen-2-yl)-[1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]-methanone

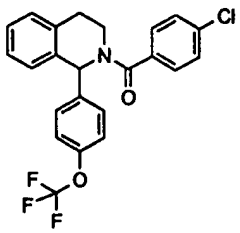


Similarly as described in example 22 using a solution of 1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 5-chlorothiophene-2-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 17.75 min. m/z: 438 (M+1)

EXAMPLE 130:

(4-Chlorophenyl)-[1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]-methanone

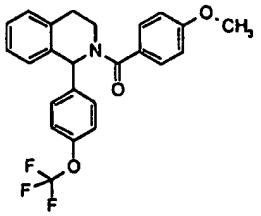


Similarly as described in example 22 using a solution of 1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-chlorobenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 17.42 min. m/z: 432 (M+1)

EXAMPLE 131:

(4-Methoxyphenyl)-[1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]-methanone

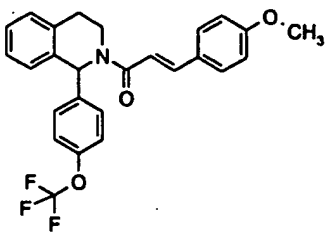


Similarly as described in example 22 using a solution of 1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 16.42 min. m/z: 428 (M+1)

EXAMPLE 132:

3-(4-Methoxyphenyl)-1-[1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]propenone

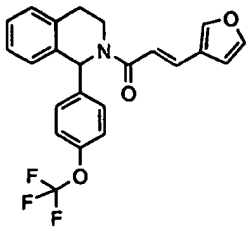


Similarly as described in example 22 using a solution of 1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxycinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 17.02 min. m/z: 454 (M+1)

EXAMPLE 133:

3-Furan-3-yl-1-[1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]propenone

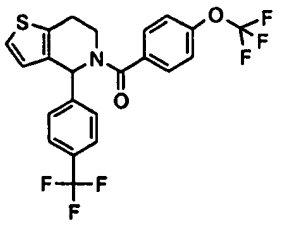


Similarly as described in example 22 using a solution of 1-(4-trifluoromethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-furan-3-ylacrylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 16.12 min. m/z: 414 (M+1)

EXAMPLE 134:

(4-Trifluoromethoxyphenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

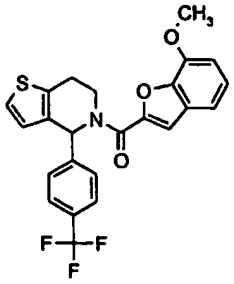


Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-trifluoromethoxybenzoic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 17.01 min. m/z: 472 (M+1)

EXAMPLE 135:

(7-Methoxybenzofuran-2-yl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

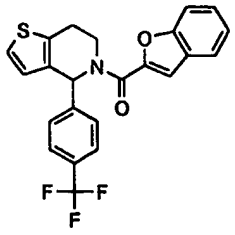


Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 7-methoxybenzofuran-2-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 16.98 min. m/z: 458 (M+1)

EXAMPLE 136:

Benzofuran-2-yl-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone

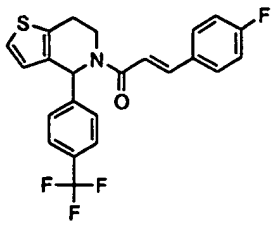


Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of benzofuran-2-carboxylic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 17.01 min. m/z: 428 (M+1)

EXAMPLE 137:

3-(4-Fluorophenyl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-propenone

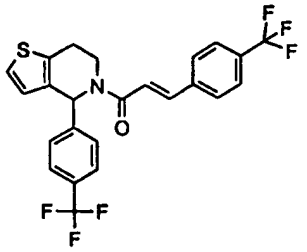


Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-fluorocinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 16.58 min. m/z: 432 (M+1)

EXAMPLE 138:

3-(4-Trifluoromethylphenyl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone

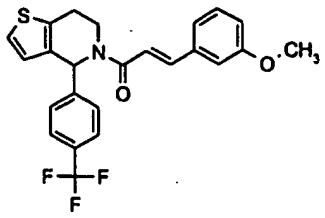


Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-trifluoromethylcinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 17.38 min. m/z: 482 (M+1)

EXAMPLE 139:

3-(3-Methoxyphenyl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone

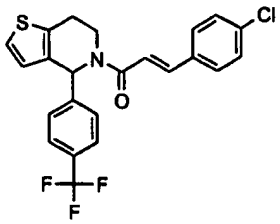


Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 3-methoxycinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 16.54 min. m/z: 444 (M+1)

EXAMPLE 140:

3-(4-Chlorophenyl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone



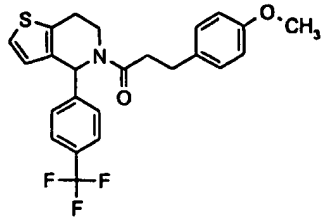
Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-chlorocinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol)

and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 17.41 min. m/z: 448 (M+1)

EXAMPLE 141:

3-(4-Methoxyphenyl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propan-1-one

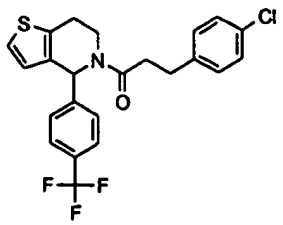


Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-methoxyhydrocinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 16.41 min. m/z: 446 (M+1)

EXAMPLE 142:

3-(4-Chlorophenyl)-1-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propan-1-one



Similarly as described in example 22 using a solution of 4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol), a solution of 4-chlorohydrocinnamic acid in N,N-dimethylformamide (0.375 M, 0.4 ml, 0.15 mmol) and 0.25 ml of a suspension of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in dichloromethane (1.73 g in 8.3 ml) affords the title compound.

HPLC-MS: R_t = 17.38 min. m/z: 450 (M+1)

General:

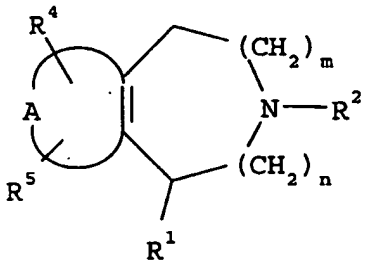
The HPLC-MS analyses were performed on a PE Sciex API 100 LC/MS System using a WatersTM 3 mm x 150 mm 3.5 µ C-18 Symmetry column and positive ionspray with a flow rate at 20 µL/minute. The column was eluted with a linear gradient of 5-90% A, 85-0% B and 10% C in 15 minutes at a flow rate of 1 ml/min (solvent A = acetonitrile, solvent B = water and solvent C = 0.1% trifluoroacetic acid in water).

The given HPLC (method B) refers to the following system:

The used HPLC-system was comprised of a Merck Hitachi L-4000 UV Detector (detection at 254 nm), a Merck Hitachi L-6200A Intelligent Pump, a Merck Hitachi AS-2000A Autosampler, and a 4 mm * 250 mm 5 µ Licrosorp RP-18 column. The compounds were eluted using a gradient of 20% to 80% acetonitrile/0.1% trifluoroacetic acid/water during 30 minutes at 1 ml/minute, followed by a gradient of 80% to 100% acetonitrile/0.1% trifluoroacetic acid/water during 5 minutes at 1 ml/minute then with 100% acetonitrile/0.1% trifluoroacetic acid during 1 minute at 1 ml/minute and 4 minutes at 2 ml/minute.

CLAIMS

1. A compound of the general formula I



wherein

A together with the double bond of formula I forms a cyclic system selected from the group consisting of benzene, thiophene, furan, pyridine, pyrimidine, pyrazine, pyridazine, pyrrole, indole, pyrazole, imidazole, oxazole, isoxazole or thiazole,

R^1 is an optionally substituted C_{1-6}-alkyl, or optionally substituted aryl,
R^2 is an optionally substituted C_{1-6}-alkyl, optionally substituted aralkyl, or COR^3,
R^3 is an optionally substituted C_{1-6}-alkyl, optionally substituted aralkyl, or optionally substituted aryl,

R^4 and R^5 independently are hydrogen, halogen, perhalomethyl, optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, nitro, cyano, amino, optionally substituted mono- or optionally substituted di-C_{1-6}-alkylamino, acylamino, C_{1-6}-alkoxycarbonyl, carboxy or carbamoyl,

n is 0, 1, or 2, and
m is 0, 1, or 2,

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

2. A compound according to claim 1, wherein A is selected from benzene or thiophene.

3. A compound according to any one of claims 1 and 2, wherein R^1 is optionally substituted phenyl.

4. A compound according to any one of the preceding claims, wherein each one of R^1, R^2, and R^3 is substituted with one or more substituents.

5. A compound according to claim 3 or 4, wherein the substituents of R^1 is halogen, perhalomethyl, perhalomethoxy, or C_{1-6}-alkoxy.

6. A compound according to claim 3 or 4, wherein the substituents of R^1 are selected from the group consisting of hydrogen, halogen, perhalomethyl, perhalomethoxy, or C_{1-6}-alkoxy.

7. A compound according to claim 5 or 6, wherein the substituents of R^1 are selected from from the group consisting of chloro, trifluoromethyl, methoxy, trifluoromethoxy.

8. A compound according to claim 3, wherein R^1 is selected from the group consisting of phenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, and 4-trifluoromethoxyphenyl.

9. A compound according to any one of claims 1 to 3, wherein R^1 is 2,3-dihydrobenzofuran or 4-methoxyphenyl.

10. A compound according to any one of the preceding claims wherein R^2 is COR^3 or $(CH_2)_q$-aryl, and q is 0, 1, 2, 3, 4, 5, or 6.

11. A compound according to claim 10, wherein R^3 is selected from the group consisting of phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, 4-(2-dimethylaminoethoxy)phenyl, or 4-(2-morpholin-4-ylethoxy)phenyl.

12. A compound according to claim 10, wherein R^3 is selected from the group consisting of 4-methylphenyl, 3,4-dimethoxyphenyl, 4-ethoxyphenyl, 4-fluorophenyl, 4-trifluoromethylphenyl, dimethylaminophenyl, 4-(2-carboxyethenyl)phenyl, 4-(2-dimethylaminoethoxy)phenyl, 4-(2-morpholin-4-ylethoxy)phenyl, 1H-indol-5-yl, 3-chloro-

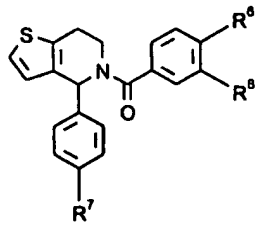
4-methoxyphenyl, and 1H-benzimidazol-5-yl.

13. A compound according to any one of the preceding claims, wherein R^4 and R^5 independently is hydrogen, chloro, or methoxy.

14. A compound according to any one of the preceding claims, wherein n is 0 or 1 and m is 0 or 1.

15. A compound according to any one of the preceding claims, wherein n is 0 and m is or 1.

16. A compound according to claim 1 and having the general formula Ia:

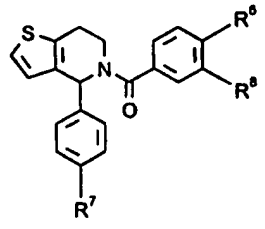


(Ia)

wherein R^7 is hydrogen, halogen, preferably chloro, methoxy, perhalomethoxy, preferably trifluoromethoxy, perhalomethyl, preferably trifluoromethyl, diloweralkylamino, preferably dimethylamino, or nitro,

and R^6 and R^8 independently are hydrogen, hydroxy, halogen, preferably chloro, bromo or fluoro, methyl, tert-butyl, phenyl, dimethylamino, methoxy, ethoxy, 2-dimethylamino-ethoxy, 2-carboxyethenyl, 2-morpholin-4-ylethoxy, perhalomethyl, preferably trifluoromethyl, perhalomethoxy, preferably trifluoromethoxy, carboxy, cyano, methylthio, methylsulfonyl, acetamido, nitro, acetyl, acetoxy, or hydroxymethyl.

17. A compound according to claim 1 and having the general formula (Ia):



(Ia)

wherein R^7 is halogen, perhalomethyl, or perhalomethoxy

and R^6 and R^8 independently are hydrogen, methoxy, ethoxy, hydroxy, fluoro, chloro, bromo, iodo, methyl, trifluoromethyl, dimethylamino, 2-carboxyethenyl, 2-

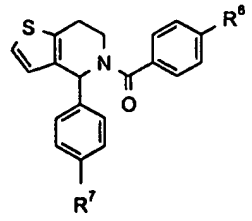
dimethylaminoethoxy, or 2-morpholin-4-ylethoxy.

18. A compound according to claim 16, wherein R^7 is selected from the group consisting of chloro, methoxy and trifluoromethyl.

19. A compound according to claim 16 or 17 wherein R^7 is trifluoromethoxy.

20. A compound according to any one of claims 17, 18 and 19, wherein R^6 and R^8 independently are hydrogen, methoxy, chloro, trifluoromethyl, 2-dimethylaminoethoxy, or 2-morpholin-4-ylethoxy.

21. A compound according to claim 1 and having the general formula (Ib):

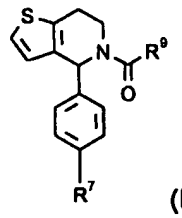


(Ib)

wherein R^7 is as described above, and

R^6 is hydroxy, halogen, preferably chloro or fluoro, methyl, dimethylamino, methoxy, ethoxy, perhalomethyl, preferably trifluoromethyl, perhalomethoxy, preferably trifluoromethoxy, cyano, methylthio, acetyl, acetoxy, or hydroxymethyl.

22. A compound according to claim 1 and having the general formula (Ic):

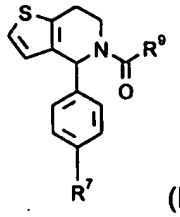


(Ic)

wherein R^7 is as defined above, and

R^9 is 4-pyridyl, 5-hydroxypyrazin-2-yl, 5-chloro-6-hydroxypyridin-3-yl, 2-chloropyridin-3-yl, benzofuran-2-yl, benzothiophen-2-yl-, 7-methoxybenzofuran-2-yl, indolyl, preferably 1H-indol-5-yl, benzimidazol, preferably 1H-benzimidazol-5-yl or thienyl, preferably 5-chlorothiophen-2-yl.

23. A compound according to claim 1 and having the general formula (Ic):

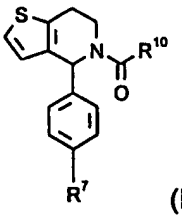


(Ic)

wherein R^7 is as defined above and R^9 is indolyl, preferably 1H-indol-5-yl or benzimidazol, preferably 1H-benzimidazol-5-yl.

24. A compound according to claim 22 wherein R^7 is as defined above and R^9 is benzothiophen-2-yl, indolyl, preferably 1H-indol-5-yl, or benzimidazol, preferably 1H-benzimidazol-5-yl.

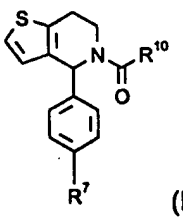
25. A compound according to claim 1 and having the general formula (Id):



(Id)

wherein R^7 is as defined above, and R^{10} is optionally substituted aralkyl as defined above, preferably 2-(4-methoxyphenyl)-ethenyl, 2-(3-methoxyphenyl)-ethenyl, 2-(4-chlorophenyl)-ethenyl, 2-(4-fluorophenyl)-ethenyl, 2-(4-trifluoromethylphenyl)-ethenyl, 2-(4-methoxyphenyl)-ethyl, 2-(4-chlorophenyl)-ethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-(2-furyl)-ethenyl, 2-(4,5-dimethyl-2-furyl)-ethenyl, 2-(5-methyl-2-furyl)-ethenyl, 2-(3-furyl)-ethenyl, 2-(2-thienyl)-ethenyl, or 2-(3-thienyl)-ethenyl.

26. A compound according to claim 1 and having the general formula (Id):

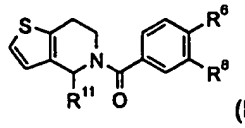


(Id)

wherein R^7 is as defined above, and R^{10} is 4-methoxyphenyl-2-ethenyl.

27. A compound according to claim 25 wherein R^7 is as defined above and R^{10} is optionally substituted aralkyl as defined above, preferably 2-(4-methoxyphenyl)-ethenyl, 2-(2-furyl)-ethenyl, 2-(5-methyl-2-furyl)-ethenyl, 2-(3-furyl)-ethenyl, or 2-(3-thienyl)-ethenyl.

28. A compound according to claim 1 and having the formula (Ie):

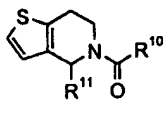


(Ie)

wherein R^{11} is pyridyl, preferably 4-pyridyl, and

R^6 and R^8 independently are hydrogen, hydroxy, halogen, preferably chloro, bromo or fluoro, methyl, tert-butyl, phenyl, dimethylamino, methoxy, ethoxy, 2-dimethylamino-ethoxy, 2-carboxyethenyl, 2-morpholin-4-ylethoxy, perhalomethyl, preferably trifluoro-methyl, perhalomethoxy, preferably trifluoromethoxy, carboxy, cyano, methylthio, methylsulfonyl, acetamido, nitro, acetyl, acetoxy, or hydroxymethyl.

29. A compound according to claim 1 and having the formula (If):

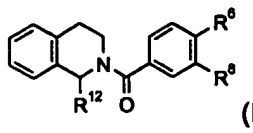


(If)

wherein R^{10} is optionally substituted aralkyl as defined above, preferably 2-(4-methoxyphenyl)-ethenyl, 2-(3-methoxyphenyl)-ethenyl, 2-(4-chlorophenyl)-ethenyl, 2-(4-fluorophenyl)-ethenyl, 2-(4-trifluoromethylphenyl)-ethenyl, 2-(4-methoxyphenyl)-ethyl, 2-(4-chlorophenyl)-ethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-(2-furyl)-ethenyl, 2-(4,5-dimethyl-2-furyl)-ethenyl, 2-(5-methyl-2-furyl)-ethenyl, 2-(3-furyl)-ethenyl, 2-(2-thienyl)-ethenyl, or 2-(3-thienyl)-ethenyl, and

R^{11} is pyridyl, preferably 4-pyridyl.

30. A compound according to claim 1 and having the formula (Ig):

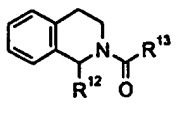


(Ig)

wherein R^{12} is aryl or aralkyl, and

R^6 and R^8 independently are hydrogen, hydroxy, halogen, preferably chloro, bromo or fluoro, methyl, tert-butyl, phenyl, dimethylamino, methoxy, ethoxy, 2-dimethylaminoethoxy, 2-carboxyethenyl, 2-morpholin-4-ylethoxy, perhalomethyl, preferably trifluoromethyl, perhalomethoxy, preferably trifluoromethoxy, carboxy, cyano, methylthio, methylsulfonyl, acetamido, nitro, acetyl, acetoxy, or hydroxymethyl.

31. A compound according to claim 1 and having the formula (Ih):



(Ih)

wherein R^{12} is aryl, preferably 4-trifluoromethoxyphenyl, or aralkyl, preferably benzyl, and

R^{13} is aralkyl as defined above, preferably 2-(4-methoxyphenyl)-ethenyl, 2-(3-methoxyphenyl)-ethenyl, 2-(4-chlorophenyl)-ethenyl, 2-(4-fluorophenyl)-ethenyl, 2-(4-trifluoromethylphenyl)-ethenyl, 2-(4-methoxyphenyl)-ethyl, 2-(4-chlorophenyl)-ethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-(2-furyl)-ethenyl, 2-(4,5-dimethyl-2-furyl)-ethenyl, 2-(5-methyl-2-furyl)-ethenyl, 2-(3-furyl)-ethenyl, 2-(2-thienyl)-ethenyl, or 2-(3-thienyl)-ethenyl.

32. A compound according to claim 1, selected from the group consisting of

(+)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 1),

(-)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 2),

(+)-[4-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-trifluoromethylphenyl)-methanone, (compound No. 3),

(-)-[4-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-trifluoromethylphenyl)-methanone, (compound No. 4),

[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 5),

(+)-[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 6),

(-)-[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 7),

[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(3-methoxyphenyl)-methanone, (compound No. 8),

(+)-[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(3-methoxyphenyl)-methanone, (compound No. 9),

(-)-[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(3-methoxyphenyl)-methanone, (compound No. 10),

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-phenyl-methanone, (compound No. 11),

(+)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-phenyl-methanone, (compound No. 12),

(-)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-phenyl-methanone, (compound No. 13),

(4-(2-Dimethylaminoethoxy)phenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 14),

(+)-(4-(2-Dimethylaminoethoxy)phenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 15),

(-)-(4-(2-Dimethylaminoethoxy)phenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 16),

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-(2-[2-morpholin-4-ylethoxy)phenyl]-methanone, (compound No. 17),

(+)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-(2-[2-morpholin-4-ylethoxy)phenyl]-methanone, (compound No. 18),

(-)-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-(2-[2-morpholin-4-ylethoxy)phenyl]-methanone, (compound No. 19),

[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-dimethylaminophenyl)-methanone, (compound No 20),

3-{4-[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine-5-carbonyl]phenyl}-acrylic acid, (compound No 21),

(4-Chlorophenyl)-[4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, both the racemate, the two pure enantiomers, and mixtures thereof (compound No 22),

[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 24),

[4-(4-Trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 25),

[4-(2-Dimethylaminoethoxy)-phenyl]-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 26),

[4-(2-Dimethylaminoethoxy)-phenyl]-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 27),

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-[4-(2-morpholin-4-ylethoxy)phenyl]-methanone, (compound No. 28),

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-[4-(2-morpholin-4-ylethoxy)phenyl]-methanone, (compound No. 29),

[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 30),

[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 31),

[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 32),

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(1H-indol-5-yl)-methanone, (compound No. 33),

(1H-Indol-5-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 34),

[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-fluorophenyl)-methanone, (compound No. 35),

[4-(4-Trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-

fluorophenyl)-methanone, (compound No. 36),
4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-[4-(2-dimethylaminoethoxy)phenyl]-methanone, (compound No. 37),
[4-(2-Dimethylaminoethoxy)phenyl]-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 38),
[7-Chloro-1-(2,3-dihydrobenzofuran-7-yl)-8-methoxy-1,2,4,5-tetrahydrobenzo[d]azepin-3-yl]-[4-(2-dimethylaminoethoxy)-phenyl]-methanone, (compound No. 39),
[4-(3,4-Dimethoxyphenyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridin-6-yl]-[4-(2-dimethylaminoethoxy)-phenyl]-methanone, (compound No. 40),
(3,4-Dimethoxyphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 41),
(3-Chloro-4-methoxyphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 42),
(4-Ethoxyphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 43),
(4-Methylphenyl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 44),
3-(4-Methoxyphenyl)-1-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]propenone, (compound No. 45),
(1H-Benzimidazol-5-yl)-[4-(4-trifluoromethoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]methanone, (compound No. 46),
or a salt thereof with a pharmaceutically acceptable acid or base.

33. A salt of a compound according to the preceding claim with a pharmaceutically acceptable base.

34. A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of claims 1 - 33, or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

35. A pharmaceutical composition for use in the treatment of diseases of the endocrinological system such as hyperglycaemia and diabetes comprising, as an active ingredient, a

compound according to any of the claims 1 - 33 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

36. The pharmaceutical composition according to claim 34 or 35 in the form of an oral dosage unit or a parenteral dosage unit.

37. A pharmaceutical composition according to claim 34 or 35 wherein said ingredient is present in a unit dose in a range from about 0.05 to 1000, preferably from about 0.1 to 500 and especially in the range from 5 to 200 mg.

38. A compound according to any of the claims 1 - 33 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use.

39. A compound according to any of the claims 1 - 33 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use in the treatment or prevention of diseases of the endocrinological system, preferably hyperglycaemia or diabetes.

40. A compound according to any of the claims 1 - 33 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form, characterized by having a glucose-6-phosphatase inhibitory activity corresponding to an IC_{50} value of less than 100 μM, preferably less than 10 μM, more preferably less than 1 μM, still more preferably less than 100 nM.

41. The use of a compound according to any of the claims 1 - 33 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form

for the preparation of a medicament.

42. The use of a compound according to any of the claims 1 - 33 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment or prevention of diseases of the endocrinological system, preferably hyperglycaemia or diabetes.

43. The use of a compound according to any of the claims 1 - 33 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment or prevention of glycogen storage disease or hypoglycaemia.

44. The use of a compound selected from the group consisting of
[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-methoxyphenyl)-methanone, (compound No. 47),
(4-Chlorophenyl)-[4-(4-chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 48),
(4-Chlorophenyl)-[4-(4-trifluoromethylphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 49),
(2-Chlorophenyl)-[4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 50),
(4-Chlorophenyl)-[4-(methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-methanone, (compound No. 51),
[4-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(4-trifluoromethylphenyl)-methanone, (compound No. 52),
(2-Chloropyridin-3-yl)-[4-(4-methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyrin-5-yl]-methanone, (compound No. 53),
[4-(4-Chlorophenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(2-thienyl)-methanone, (compound No. 54),
[4-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl]-(2-thienyl)-methanone, (compound No. 55),
(4-Chlorophenyl)-(4-propyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridin-5-yl)-methanone,

(compound No. 56).

or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament.

45. The use of a compound selected from the group of compounds of the preceding claim for the preparation of a medicament for the treatment or prevention of diseases of the endocrinological system.

46. The use of a compound selected from the group of compounds of claim 44 for the preparation of a medicament for the prevention or treatment of hyperglycaemia or diabetes, preferably NIDDM.

47. A method for the treatment of ailments in a subject in need thereof comprising administering an effective amount of a compound according to any one of claims 1-33, and 44, or of a composition according to any one of the preceding composition claims, to said subject.

48. A method of treating or preventing diseases of the endocrinological system, preferably hyperglycaemia or diabetes in a subject in need thereof comprising administering an effective amount of a compound according to any one of the preceding compound claims to said subject.

49. A method of treating or preventing hyperglycaemia or hypoglycaemia in a subject in need thereof comprising administering an effective normoglycaemic amount of a pharmaceutically acceptable salt of a compound according to any one of the preceding compound claims, or of a composition according to any one of the preceding composition claims, to said subject.

50. A process for the manufacture of a medicament, particular to be used in the treatment or prevention of diseases of the endocrinological system, such as, hyperglycaemia, diabetes, hypoglycaemia, and glycogen storage disease, which process comprises bringing a compound according to any of the claims 1-33, and 44 or a pharmaceutically accept-

able salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form thereof, into a galenic dosage form.

51. Any novel feature or combination of features as described herein.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00083

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 495/04, C07D 217/06, A61K 31/435, A61K 31/47
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9634870 A1 (SYNTHELABO), 7 November 1996 (07.11.96) --	1-46,50-51
X	WO 8705295 A1 (UNIVERSITE LOUIS PASTEUR), 11 Sept 1987 (11.09.87) --	1-46,50-51
X	EP 0088250 A2 (BOEHRINGER INGELHEIM KG), 14 Sept 1983 (14.09.83), see claims 1, 2 --	1-3,6-8,13, 14-15,51
X	US 4681888 A (ANDRE ESANU), 21 July 1987 (21.07.87), see claim 1 --	1-3,5-7,13, 14-15,51

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 1998	26 -06- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00083

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0157324 A2 (BAYER AG), 9 October 1985 (09.10.85) -- --------	35-46,50

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00083

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-15, 51
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 1-15 and 51 are too broadly formulated and do not comply with Art. 6. PCT prescribing that claims shall be clear and concise. For this reason the search has been limited to claims 16-32 and 44.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/DK 98/00083

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		NO 975020 A	05/01/98
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/DK 98/00083

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